WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS
ON THE
EVALUATION OF CARCINOGENIC RISK
OF CHEMICALS TO MAN
Some inorganic and organometallic compounds
VOLUME 2

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER
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IARC MONOGRAPHS

ON THE

EVALUATION OF THE CARCINOGENIC

RISK OF CHEMICALS TO MAN:

Some inorganic and organometallic compounds

Volume 2

This publication is the outcome of the
meeting of two IARC Working Groups on the
Evaluation of the Carcinogenic Risk of Chemicals to Man,
Lyon, 7 October and 29 November - 4 December 1972

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Lyon, 7 October 1972

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Lyon, 29 November - 4 December 1972

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BACKGROUND AND PURPOSE OF THE IARC PROGRAMME ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN

In the past few years the number and quantity of chemicals in the environment has increased. The possible adverse effect of these chemicals on human health is a matter of international concern. The International Agency for Research on Cancer (IARC) has consequently initiated a programme on the evaluation of carcinogenic risk of chemicals to man which was supported by a Resolution of the Governing Council at its Ninth Session concerning the role of the Agency in providing government authorities with expert, independent scientific opinion on environmental carcinogenesis. As one means to this end, the Governing Council recommended that the Agency should continue to prepare monographs on the carcinogenic risk of individual chemicals to man.

In view of the importance of this programme and in order to expedite the production on monographs, the National Cancer Institute of the United States has provided IARC with additional funds for this programme.

The objective of this programme is to achieve and publish a balanced evaluation of data through the deliberations of an international group of experts in chemical carcinogenesis and to put into perspective the present state of knowledge with the final aim of evaluating the data in terms of possible human risk, as well as to indicate the need for research efforts to close our gaps in knowledge.

SCOPE OF THE MONOGRAPHS

In 1972 the first volume of these monographs was published[1]. These monographs summarise the evidence for the carcinogenicity of individual chemicals in a condensed uniform manner for easy comparison. The data were compiled, reviewed and evaluated by a working group of experts. No recommendations are given concerning preventive measures or legislation,

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[1] International Agency for Research on Cancer (1972) IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, 1, Lyon

since these matters depend on risk-benefit evaluation, which seems best made by individual governments and/or international agencies such as WHO and ILO.

Whereas the first volume covered a number of substances belonging to different chemical groups, the second volume is devoted to one class, namely inorganic and organometallic compounds.

As new data on chemicals for which monographs have already been written and new principles for evaluation become available, re-evaluation will be made at future meetings, and revised monographs will be published as necessary. Special meetings can be called to evaluate important compounds for which the data are controversial and there seems to be an urgent need for action by public health authorities. The monographs will be distributed to international and governmental agencies, will be available to industries and scientists dealing with these chemicals, and will form the basis of advice from IARC on carcinogenesis from these substances.

MECHANISM FOR PRODUCING THE MONOGRAPHS

As a first step a list of chemicals for possible consideration by the Working Group was established. IARC collected pertinent references regarding physico-chemical characteristics, use and occurrence, as well as pharmacological, toxicological and epidemiological data on these compounds. Assistance in collecting data on use and occurrence was provided by the Stanford Research Institute and the Occupational Health Unit of WHO. The material was first summarised by an expert consultant or an IARC staff member, who prepared the first draft monograph, which in some cases was then sent to another expert for comments. This draft was circulated to all members of the Working Group about two months before the meeting, at which time it was critically reviewed. Further additions to and deletions from the data were agreed upon and a final version of comments and evaluation on each compound was adopted.

Priority for the Preparation of Monographs

Priority for consideration was given mainly to chemicals for which some adequate experimental evidence of carcinogenicity existed and/or for

which there was evidence of human exposure. However, neither human exposure nor potential carcinogenicity could be judged until all the relevant data had been collected and examined in detail. The inclusion of a particular compound in a monograph did not necessarily mean that the substance was considered to be carcinogenic. Equally, the fact that a substance had not yet been considered did not imply that it was non-carcinogenic.

Data on which the Evaluation was Based

With regard to the biological data, only published articles or papers already accepted for publication were reviewed. Every effort was made to cover the whole literature, but some studies may have been inadvertently overlooked. Since the monographs contain only the relevant data the reader is unable to judge whether or not a particular work was considered. It is therefore important that research workers who are aware of important data which may change the evaluation make them available to the Unit of Chemical Carcinogenesis of the International Agency for Research on Cancer, Lyon, France, in order that they can be considered for a possible re-evaluation.

The Working Group

The members of the Working Group who participated in the consideration of particular substances are listed at the beginning of this publication. Each monograph bears a footnote indicating the date of the meeting at which it was considered. The members of the Working Group were invited by IARC to serve in their individual capacities as scientists, and not as representatives of their governments or of any institute to which they were affiliated.

GENERAL REMARKS ON THE EVALUATION

Terminology

The term "chemical carcinogenesis" in its widely accepted sense is used to indicate the induction or enhancement of neoplasia by chemicals. It is recognised that, in the strict etymological sense, this term means the induction of cancer. However, common usage has led to its employment in denoting the induction of various types of neoplasm. The terms

"tumourigen", "oncogen" and "blastomogen" have all been used synonymously with "carcinogen", although occasionally "tumourigen" has been used specifically to denote the induction of benign tumours.

Response to Carcinogens

For present practical purposes, no distinction is made between the induction of tumours and the enhancement of tumour incidence, although it is noted that there may be fundamental differences in mechanisms that will eventually be elucidated.

The response to a carcinogen in experimental animals may be observed in several forms:

(a) as a significant increase in the frequency of one or several types of neoplasm as compared to the control;
(b) as the occurrence of neoplasms not observed in control animals;
(c) as a decreased latent period as compared with control animals;
(d) as a combination of (a) and (c).

Qualitative Aspects

The qualitative nature of neoplasia has been much discussed. Many instances of carcinogenesis involve the induction of both benign and malignant tumours. There are few, if any, recorded instances in which only benign tumours are induced; their occurrence in experimental systems indicates that the same treatment may increase the risk of malignant tumours also.

In experimental carcinogenesis, the type of cancer seen is often the same as that recorded in human studies (e.g., bladder cancer in man, monkeys, dogs and hamsters after administration of 2-naphthylamine). In other instances, however, a chemical will induce different neoplasms or neoplasms at different sites in different animal species (e.g., benzidine, which induces hepatic carcinoma in the rat, but bladder carcinoma in man).

Purity of the Compound Tested

The Working Group was often faced with lack of information on the purity of the compounds tested. In order to render better judgement as to whether the compound itself or the impurity is responsible for the carcinogenic effect, detailed specification of the substance under test is essential.

Quantitative Aspects

Dose-response studies are important in the evaluation of human and animal carcinogenesis. Sometimes, the only way in which a causal effect can be established with confidence is by the observation of increased incidence of neoplasms over the control in relation to increased exposure. It is hoped that, eventually, dose-response data may be used for assessment in carcinogenesis in the same way that they are used in general toxicological practice.

Extrapolation from Animals to Man

No attempt has been made to interpret the animal data in the absence of human data in terms of possible human risk; and no distinction has been made between weak and strong carcinogens, since no objective criteria are at present available to do so. These monographs may be reviewed if some such criteria should be elaborated. In the meantime, the critical assessment of the validity of the animal data given should help national and/or international authorities to make decisions concerning preventive measures or legislation in the light of WHO recommendations on food additives[1], drugs[2] and occupational carcinogens[3].

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[1] Wld Hlth Org. techn. Rep. Ser., 1961, No. 220, pp. 5, 18 and 19

[2] Wld Hlth Org. techn. Rep. Ser., 1969, No. 426, pp. 19, 21 and 22

[3] Wld Hlth Org. techn. Rep. Ser., 1964, No. 276, pp. 29 and 30

Evidence of Carcinogenicity to Humans

Evidence that a particular chemical is carcinogenic in man depends on clinical and epidemiological data, which may be in the main descriptive, retrospective or prospective.

Descriptive studies may identify a cluster or a change in rates for a particular neoplasm in a subgroup of the population, which suggests the influence of carcinogens in the environment. Retrospective studies (i.e., case-control studies that go into the histories of persons with or without cancer) have revealed occupational carcinogens (e.g., shale oil, chromates, asbestos, 2-naphthylamine, benzidine) or iatrogenic carcinogens (e.g., chlornaphazin, thorotrast, oestrogens).

Once a relationship is known or suspected between an exposure and cancer, prospective studies (i.e., follow-up or cohort studies of exposed and unexposed groups) will identify more precisely the magnitude of the risk and may clarify time relationships, dose-response effects and other details of cancer induction. Wherever possible the Working Group considered evidence of the influence of variables other than the agent under suspicion in inducing the cancer under study (e.g., cigarette-smoking in the study of lung cancer among asbestos workers).

Finally, if man does develop cancer from a specific chemical, its removal from the environment should be followed eventually by epidemiological evidence of a decline in the frequency of the neoplasm in the exposed group.

Mixtures and Groups of Carcinogens

Mixtures of chemicals are sometimes associated with the occurrence of cancers in man, but no information is available on the specific components. Continuing efforts should be made to elucidate the roles of the various components, and of impurities in substances, to assist in planning better preventive measures and to provide a basis for assessing similar hazards. There are situations where carcinogens may occur in groups in the human environment and where it is not yet possible to attribute the observed effects to individual substances. This is notably so in the case of the

polycyclic aromatic hydrocarbons and certain aromatic amines.

EXPLANATORY NOTES ON THE MONOGRAPHS

In sections 1, 2 and 3 of each monograph, except for minor remarks, the data are recorded as given by the author; whereas the comments by the Working Group are given in section 4, headed "Comments on data reported and evaluation".

Title of the Monograph

Each monograph refers to chemicals or groups of similar chemicals for which one evaluation was made. The title therefore uses the chemical name(s) of the substance(s) or a group name. Whenever possible the chemical abstract name is used.

Chemical and Physical Data (section 1)

Chemical and physical properties include data that might be relevant to carcinogenicity (for example, lipid solubility) and those that concern identification. Where relevant, data on solubility, volatility and stability are indicated. All data except those for "Technical products and impurities" refer to the pure substances.

Use and Occurrence (section 2)

The analytical data recorded under "Occurrence" are dependent on the methods employed. In some instances, the quantitative and even the qualitative results may be questionable because the methods were not satisfactory. Data on human exposure are also included, where available, under this heading.

Biological Data Relevant to the Evaluation of Carcinogenic Risk to Man (section 3)

As pointed out earlier in this introduction, the monographs are not intended to itemise all studies reported in the literature. Although every effort was made to review the whole literature, some studies were purposely omitted (a) because of their inadequacy (e.g., too short a

duration, too few animals, poor survival or too small a dose)[1], (b) because they only confirmed findings already reported or (c) because they were judged irrelevant for the purpose of the evaluation. The data recorded here are summarised as given by the author. However, certain shortcomings of reporting or experimental design are also mentioned, and minor comments by the Working Group are given in brackets. The essential critical comments by the Working Group are, however, made in Section 4 ("Comments on data reported and evaluation"), with the exception of minor comments given in brackets.

Carcinogenicity and related studies in animals (3.1)

Mention is made of all routes of administration by which the compound has been tested and all species in which the chemical has been investigated. In some cases where similar results were obtained by other authors and/or other laboratories, reference is made to a summary article. Quantitative data are given in so far as they will enable the reader to realise the order of magnitude of the effective dose. The doses are indicated as they appear in the original paper. In general, negative experiments of an inadequate standard[1] are not summarised. In certain cases, however, it was felt that such data should be included since they would contribute to the total picture.

Other relevant biological data (3.2)

The data reported in this section are divided into three categories: (a) information on the metabolic fate in animals, including localisation into tissues, (b) similar information on man and (c) comparison of animal and human data. Data on acute toxicity are included when considered relevant.

Observations in man (3.3)

Epidemiological studies are summarised. This sub-section also includes, where relevant, summaries of reports of cases of cancer in man that have been related to possible exposure to the chemical.

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[1] Wld Hlth Org. techn. Rep. Ser., 1958, No. 144; 1961, No. 220; 1967, No. 348

Comments on Data Reported and Evaluation (section 4)

This section includes the critical view of the Working Group on the data reported. It is purposely kept as brief as possible since it should be read in conjunction with the data recorded.

Animal data (4.1)

The animal species mentioned are those in which the carcinogenicity of the substances was clearly demonstrated, irrespective of the route of administration. Adequate negative data are considered. When inadequate studies are mentioned, comments on their limitations are included. Routes of administration used in experimental animals that are similar to possible human exposures (ingestion, inhalation and skin exposures) are given particular mention. In most cases, tumour sites are also indicated. If the substance has produced tumours on pre-natal exposure or in single-dose experiments, this is also indicated. This sub-section should be read in the light of comments made in the section "Extrapolation from animals to man" of this introduction.

Human data (4.2)

In some cases, a brief statement is made on the possible exposure of man. The significance of epidemiological studies and case reports is discussed and the data are interpreted in terms of possible human risk.

SPECIAL REMARKS ON THE SUBSTANCES CONSIDERED IN THIS VOLUME

In the first volume of this series[1], monographs were prepared on chemicals from different chemical groups in order to examine the feasibility of this project, and to investigate the problems which may be encountered when evaluating chemicals of completely different chemical structures or different uses and occurrences.

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[1] International Agency for Research on Cancer (1972) IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, 1, Lyon

The groups of compounds considered in the present volume have been chosen because data on epidemiological and/or experimental studies on carcinogenesis were available. The fact that a substance has been considered does not necessarily mean that it is carcinogenic, nor that a related substance which has not been considered in the present volume is necessarily not carcinogenic.

THE MONOGRAPHS

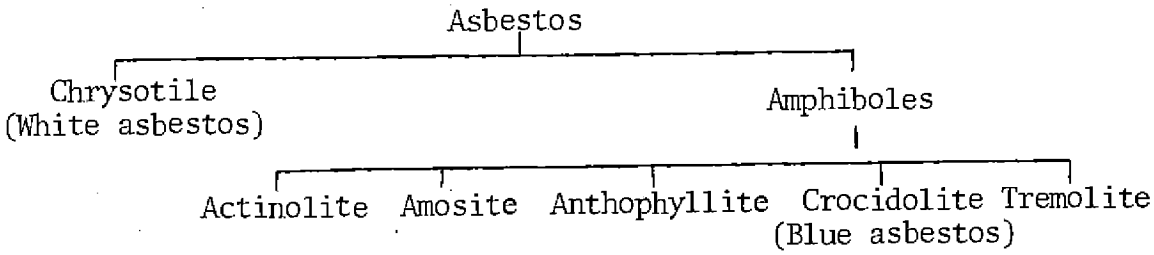
ASBESTOS*

1. Chemical and Physical Data

1.1 Definition and classification

Asbestos is the generic name given to a class of natural fibrous silicates which vary considerably in their physical and chemical properties.

The minerals are classified as follows:



Chrysotile is by far the most abundant form of asbestos. Only chrysotile, anthophyllite, amosite and crocidolite are of commercial importance.

1.2 Synonyms

Chem. Abstr. Nos.:	Chrysotile	12001 - 29 - 5
	Amosite	12172 - 73 - 5
	Anthophyllite	17068 - 78 - 9
	Crocidolite	12001 - 28 - 4

* Considered by the Working Group in Lyon, October 1972.

1.3 Chemical and physical properties

(a) General :

TABLE 1

PROPERTY	CHRYSOTILE	AMOSITE	ANTHOPHYLLITE	CROCIDOLITE
Mineral Association [B]	In altered peridotite adjacent to serpentine and limestone near contact with basic igneous rocks	In crystalline schists, etc [H] Banded ironstones	In crystalline schists and gneisses	Iron-rich siliceous argillite in quartzose schists [H] Banded ironstones
Essential Composition [B]	Hydrous silicates of magnesia	Silicate of Fe and Mg Higher iron than anthophyllite	Mg silicate with iron	Silicate of Na and Fe with some water
Idealised Chemical Formula [MC]	$Mg_3Si_2O_5(OH)_4$	$(Fe^{++}Mg)_7$ $Si_8O_{22}(OH)_2$	$(MgFe^{++})_7$ $Si_8O_{22}(OH)_2$	$Na_2Fe_3^{++}Fe_2^{+++}$ $Si_8O_{22}(OH)_2$
		where cations are written in parentheses without subscripts, a variable composition is indicated with the most abundant species first		
Colour [B]	White, grey, green, yellowish	Ash grey, greenish or brown	Greyish white, brown-grey, or green	Lavender, blue, greenish
Hardness, MOHS [B]	2.5 - 4.0	5.5 - 6.0	5.5 - 6.0	4
Specific Gravity [H]	2.55	3.43	2.85 - 3.1	3.37

Tensile Strength kg/cm^2 H	31,000	25,000	<5,000	35,000
Young's Modulus kg/cm^2 H	1.65×10^6	1.65×10^6	-	1.9×10^6
Length BH	Short to long	Long	Short	Short to long
Texture B	Soft to harsh Also silky	Coarse, but somewhat pliable	Harsh	Soft to harsh
Flexibility B	Very flexible	Good, less than chrysotile	Very brittle Non-flexible	Fair to good
Fusibility B	Fusible at 1710°C	Fusible at 1575°C, loses water at moderate temperatures	Fusible at 1650°C	Fusible at 1335°C
Cleavage H	010 perfect B	210 perfect	210 perfect	210 perfect
Extinction H	Parallel	Parallel	Parallel	Parallel
Birefringence H	Moderate first-order	Strong second-order	Moderate low second-order	Weak (masked)
Refractive Index $\eta\alpha$ H	1.493-1.553	1.657-1.688	1.578-1.652	1.685-1.698
Refractive Index $\eta\gamma$	1.517-1.557	1.675-1.717	1.591-1.676	1.689-1.703

Electric Charge [B]	Positive	Negative	Negative	Negative
Maximum solubility in HCl : % loss in wt [B]	56.00	12.00	2.13	3.14
Maximum solubility in NaOH : % loss in wt [B]	1.03	6.82	1.77	1.20

Compiled from Badollet[B] (1961), Hodgson[H] (1965) and Morgan & Cralley[MC] (1963).

(b) Chemical composition :

Data on the chemical composition of different types of asbestos from various locations have been reported by a number of authors, including Sinclair (1959), Hodgson (1966), Speil & Leineweber (1969), Timbrell (1970a), Morgan & Cralley (1973).

Speil & Leineweber (1969) give the chemical compositions of commercial chrysotile from various locations and point out that these differ very little from the idealised composition of $Mg_3(Si_2O_5)(OH)_4$. The impurities which are present in chrysotile may be part of the crystal structure or due to associated minerals. The most common impurity is iron, and the next aluminium; other impurities associated with chrysotile in lesser amounts are calcium, chromium, nickel, manganese, sodium and potassium.

Information on the chemical composition of the amphibole types of asbestos varies appreciably according to the source of the fibres.

Morgan & Cralley (1973) have reported trace element analyses of asbestos from various deposits. Table 2 is a selection of their results.

TABLE 2

Levels of trace metals in samples of asbestos from various regions

Source	Fe (%)	Cr	Co	Mn (mg/kg)	Ni	Sc
CHRYSOTILE						
Rhodesia	1.7	1390	55	450	1360	6
Canada	2.6	490	50	480	820	5
Cyprus	3.1	340	54	720	870	2
AMOSITE						
South Africa	High	35	7	11800	<100	5
CROCIDOLITE						
NW Cape (Mine A)	High	<20	0.6	240	<100	<0.1
" (Mine B)		<20	0.4	170	<100	0.3
Transvaal (Mine A)		20	0.8	140	<100	0.6
" (Mine B)		<20	0.6	220	<100	0.3
ANTHOPHYLLITE						
Finland	4.4	870	50	1060	1360	5

International reference samples[1] of Canadian chrysotile, Rhodesian chrysotile, amosite, anthophyllite and crocidolite, suitable for biological studies and other purposes, have been prepared under the auspices of the UICC (Timbrell et al., 1968; Timbrell, 1973a).

(c) Fibre structure:

The crystal structure of chrysotile asbestos, first determined by Warren & Bragg (1930) and later elucidated by Warren & Herring (1941), has been the subject of extensive research in recent years (Whittaker, 1953, 1955, 1956 a, b, c, 1957; Maser et al., 1960; Yada, 1967). The basis of the structure is an infinite silica sheet $(Si_2O_5)_n$ in which all the silica tetrahedra point in the same direction (See Fig. 1). Attached to one side of this sheet is a brucite $Mg(OH)_2$ layer in which two out of every three hydroxyls are replaced by the apical oxygens of the silica tetrahedra. A mismatch in the dimensions of the double sheet introduces a strain into the structure which is relieved by curvature, resulting in the hollow cylindrical morphology of the chrysotile fibrils. Fibril diameters vary between about 10 and 80 nm, but the mean values are generally in the range of 30-40 nm (Atkinson et al., 1971). Chrysotile fibres consist of bundles of fibrils and usually exhibit a curved and twisted morphology in air samples and in histological sections (Timbrell, 1970b).

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[1] These samples may be obtained from:

National Research Institute for Occupational Diseases
Joubert Street Ext.
Civic Centre
Johannesburg
South Africa

or Medical Research Council Pneumoconiosis Unit
Llandough Hospital
Penarth
Glamorgan
CF6 1XW
UK

The structure of tremolite as determined by Warren (1929) serves as a model for the amphiboles. The basic structural unit is a double silica chain (Si_4O_{11}). As in the chrysotile sheets, all of the silica tetrahedra point in one direction (See Fig. 2). These chains are paired 'back-to-back' with a layer of hydrated cations in between, the final structure being formed by the stacking of these sandwich ribbons in an ordered array. The various members of the amphibole group are characterised by the different cations which occur in the structure; the principal cations are magnesium, iron, calcium and sodium.

Amosite, anthophyllite and crocidolite fibres in air samples and histological sections are generally straight (Timbrell, 1970b; Timbrell et al., 1970). Timbrell et al. (1971) have reported electron microscope studies on fibres from milled rock specimens. North-western Cape crocidolite samples gave very similar fibre-diameter distributions. Transvaal crocidolite closely resembled Transvaal amosite but differed markedly from crocidolite from other sources where the fibres are finer and shorter.

(d) Magnetic properties:

Magnetite occurs as an impurity in most chrysotile deposits (Badollet, 1961) and can be separated magnetically. Timbrell (1972a) has shown that fibres of amosite, anthophyllite and crocidolite, which contain structural iron, exhibit preferred orientations in magnetic fields when in liquid or air suspension. Fibres from different sources show different responses.

(e) Technical products and impurities:

Some samples of asbestos have been shown to contain appreciable amounts of primary (natural) oils which may contain polycyclic hydrocarbons such as benzo(a)pyrene (Harington, 1962; Harington & Roe, 1965; Pylev & Shabad, 1973). Secondary oils may be present as a result of contamination during processing and transport. Metals may find their way on to the minerals during industrial or laboratory milling. Hammer milling may increase considerably the nickel, chromium, cobalt and iron content.

2. Use and Occurrence

(a) Use

Asbestos has been used for thousands of years. The modern industry dates from about 1880, when it was introduced to make heat- and acid-resistant fabrics. There are now hundreds of valuable applications (Hendry, 1965; Hueper, 1966). Most of it goes to the building industry to strengthen cement and plastics. It is also very widely distributed, in sheet and sprayed form, for heat insulation and sound absorption. Asbestos is an essential constituent of brake shoes and clutch plates, and it has valuable filtration properties. Asbestos cloths are used extensively for fire protection, including the cladding of structural steel beams.

Chrysotile accounts for over 95% of the asbestos used. Other types of fibre have valuable special properties. Corcidolite (3% of the total) has been used in ship building since 1900, because of its good resistance to acids and to sea water. Very large amounts were used for spraying in naval vessels during and after World War II. Crocidolite is also used in mixture with chrysotile to accelerate the production of asbestos pressure pipes and sheeting. Amosite bonds well with plastics and is used in floor tiles, in fireproof-boards in ships, and for spray-insulation. Anthophyllite is a talc-like form of asbestos and is used as an industrial talc and in paper-making. The world production of asbestos has increased ten-fold over the last 40 years and now exceeds 4,000,000 tons per annum.

(b) Detection of asbestos

Procedures for the sampling and measurement of airborne asbestos dust by the membrane filter method have been described (Asbestosis Research Council, 1971 a, b). For the study of asbestos in tissues the use of electron-microscopy is essential (see section 3.2).

(c) Occurrence

Chrysotile: The largest commercial deposits are in the Ural Mountains and in Quebec Province. It is also mined in British Columbia, China, Cyprus, Italy, Southern Africa and the USA.

Crocidolite: Most of the fibre comes from the North-western Cape and Transvaal areas of South Africa. In the past small amounts have been mined in Western Australia and Bolivia.

Amosite: Transvaal, South Africa, is the only source of this type of fibre.

Anthophyllite: This form of asbestos is found mainly in Finland.

Talc: This is a term used to describe a group of minerals - sometimes a mixture of several - which have a slippery feel when rubbed between the fingers. It is used for a wide variety of purposes and is divided into two main commercial types - toilet and industrial talc. Toilet talc is mined in deposits where there is little or no contamination by asbestiform minerals. The material contains very few or no microscopic fibres. Industrial talc is often a mixture of several minerals including fibrous forms, e.g., tremolite. It is used as a parting and lubricating powder in many industries, especially in rubber and cable manufacture. It is also used as a filler in paints, paper and plastics.

Asbestos is widely distributed in the environment. Serpentine, of which chrysotile is the fibrous form, is a common mineral. Very small amounts of asbestos (0.1 ng/m^3 to 100 ng/m^3) are present in the general atmosphere (Nicholson & Pundsack, 1973). However, much heavier pollution of the air by asbestos dust occurs in the vicinity of asbestos mines, and high levels have been recorded near some factories. The widespread use of asbestos for insulation and as a structural component of buildings results in a potential source of air contamination while construction, alterations and demolition are in progress. Significant exposures to asbestos dust have occurred during its transport, the shaking out of sacks, the cleaning of containers and from dusty clothing.

Minute quantities of fibre are present in water, beverages and pharmaceutical preparations when asbestos filters have been used in the purification of these fluids (Cunningham & Pontefract, 1971; Nicholson et al., 1972).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Man

3.1 Carcinogenicity studies in animals

(a) Inhalation and/or intratracheal administration

Inhalation experiments

Mouse: Lynch et al. (1957) exposed AC/F_1 hybrid mice by inhalation to a commercial preparation of chrysotile asbestos and observed a higher incidence of animals with multiple pulmonary adenomas in the exposed group (58/127 in the test group compared with 80/222 in the controls).

Rat: Gross et al. (1967) observed carcinomas of the lung in rats repeatedly exposed to chrysotile dust of a mean concentration of 86 mg/m^3 for 30 hours per week. Out of 72 rats surviving for 16 months or longer, 20 developed adenocarcinomas and four squamous cell carcinomas, while no tumours occurred in 39 controls. The authors suggested that the presence of trace metals from the hammers of the mill used to prepare the fibre was a factor in the induction of these tumours.

Reeves et al. (1971) found squamous carcinomas in 2/31 rats which survived exposure to crocidolite for two years at a concentration of 49 mg/m^3 for 16 hours per week. Five rats exposed to chrysotile developed pulmonary adenomatosis, but no malignant tumours were observed amongst rats exposed to either chrysotile or amosite.

Wagner (1972) exposed groups of C/D Wistar rats to the five UICC asbestos samples at a concentration of 12 mg/m^3 of respirable dust[1] at two lengths of exposure, 233 rats for one day (seven hours) and 182 rats for three months (450 hours). At the end of the three-month period of exposure the amount of dust in the lungs of the animals exposed to chrysotile was only one-sixth of that found in the animals exposed to the three amphibole samples. Mesotheliomas were

[1] Dust which penetrates deeply into the lung and is deposited beyond the ciliated epithelium.

observed in three rats, one with amosite and one with crocidolite after the shorter exposure, and a third peritoneal tumour was found in a rat which had undergone the longer exposure to crocidolite. One squamous carcinoma of the lung was seen in the long exposure crocidolite group. A significant excess of adenomas compared with the non-exposed controls was observed with the longer exposure for all dusts except anthophyllite.

This experiment has been supplemented by one with exposures for up to two years. All types of fibre produced asbestosis, which was progressive after removal from the dust. Also, all UICC samples, including anthophyllite, produced an excess of lung tumours. These tumours were mainly adenomas. Adenocarcinomas, squamous cancers and the occasional mesothelioma were also produced (Wagner & Berry, 1973).

Intratracheal injection has been used to study the cocarcinogenesis of chrysotile fibre with benzo(a)pyrene in rats by Vôsamäe (1972) and Pylev (1972) and in hamsters by Miller et al. (1965). The experiments demonstrated that chrysotile promoted the carcinogenicity of benzo(a)pyrene (IARC, 1973).

(b) Intraperitoneal administration

Rat: Intraperitoneal injection of asbestos can cause peritoneal mesotheliomas. Reeves et al. (1971), using a dose of 20 mg in Charles River C/D rats, produced these tumours with crocidolite and chrysotile but not with amosite.

(c) Other experimental systems

Intrapleural adminstration: All commercial types of asbestos have produced mesotheliomas in C/D Wistar rats. A dose of 20 mg of the five UICC standard reference samples (see section 1.3b) produced mesotheliomas in varying numbers - crocidolite 61%, amosite 36%, anthophyllite 34%, Canadian chrysotile 30% and Rhodesian chrysotile 19% (Wagner & Berry, 1973). Stanton & Wrench (1972), with a dose of 40 mg of asbestos dust on gelatine-coated fibre-glass pledgets, found that three of the UICC samples, crocidolite, amosite and

Rhodesian chrysotile, all produced mesotheliomas in about 60% of their Osborne-Mendel rats. Pylev & Shabad (1973) induced mesotheliomas with 60 mg of Russian chrysotile. In all these studies there was a long latent period between inoculation and appearance of the tumours. Evidence that the response was dose related was provided by Wagner et al. (1970) and by Stanton & Wrench (1972). Mesotheliomas have also been produced by other workers: in rats (Donna, 1970; Reeves et al., 1971), in hamsters (Smith et al., 1965) and in rabbits (Reeves et al., 1971).

The suggestion has been made that natural oils and waxes (Harington, 1962) and contaminant oils from milling of the fibre (Harington & Roe, 1965; Roe et al., 1966) or from plastic storage bags (Commins & Gibbs, 1969) contributed to the tumours. But crocidolite from which the oils had been removed gave very similar results to untreated fibre (Wagner & Berry, 1969). This has been confirmed for all five UICC samples from which the oils were removed. The untreated and the oil-extracted fibre produced mesotheliomas in 56 and 58 out of 160 C/D Wistar rats in each group respectively (Wagner, 1972).

The fibre diameter, length and shape may be important. All of the eight separate sub-samples which were pooled in the UICC Canadian chrysotile reference sample (Timbrell & Rendall, 1972), when ground separately to a finer powder, produced higher incidences of mesotheliomas than the pooled sample. The highest incidence, 66%, was produced by a superfine sample (dose 20 mg) produced from Grade 7 by water sedimentation (Wagner & Berry, 1969). However, Stanton & Wrench (1972) found that UICC crocidolite when partially pulverised gave fewer mesotheliomas than did the standard sample. Prolonged fine grinding is known to destroy fibre and crystalline structure (Occella & Maddalon, 1963). Stanton (1973) showed that fibres of other materials, including glass, could induce mesotheliomas, but only when the diameter was of the same order as that of asbestos. The possible importance of physical factors in tumour induction has been discussed by Timbrell (1973b).

3.2 Other relevant biological data

Asbestos is not very soluble, thus most of the fibres retained in tissues within the body remain unaltered. Some become coated with iron-containing protein to form characteristic asbestos bodies (Davis & Gross, 1973). These form more readily on amphiboles (Pooley, 1973), although many fibres remain free of this coating. Chrysotile fibres tend to break up into submicroscopic fibrils. Langer et al. (1970) and Morgan et al. (1971) showed in vivo that magnesium is leached out of the crystal lattice of chrysotile. Amphiboles apparently remain unaltered. Morgan & Holmes (1970) and Morgan et al. (1971) showed that when asbestos was inoculated intrapleurally, the majority of the fibre was cleared during the first ten days; but subsequently there was a very slow elimination through the gut. In feeding experiments almost all the fibre was eliminated. After intrapleural or subcutaneous inoculation, the only translocation that occurred was of a minute fraction of the finer fibres. This evidence was supported by the studies of Kanazawa et al. (1970). Occasional asbestos fibres or bodies have been reported in other tissues, including pancreas, spleen and thyroid. There is no information on how the fibres reach these sites.

Following inhalation, asbestos fibres found in sections of lung tissue are usually <3 μm in diameter and <100 μm in length. Thicker or longer fibres are either not inhaled or are rapidly cleared from the respiratory tract. On a weight basis, only a very small proportion of inhaled fibre is retained. An account of the inhalation of fibres is given by Timbrell (1965, 1972b). Electron-microscopy is essential for studies of asbestos in tissue as many of the fibres of chrysotile and some of the amphiboles are too small in diameter to be seen with the light microscope (Langer & Pooley, 1973).

In early experiments, it was demonstrated that exposure of guinea pigs and monkeys to the four commercial types of asbestos produced fibrotic lesions of the lung and pleura similar to those seen in human cases of asbestosis (Vorwald et al., 1951; Wagner, 1963; Holt et al., 1965). In more recent experiments this finding has been confirmed in rats (Wagner & Berry, 1973).

3.3 Observations in man

(a) Lung pleural and peritoneal cancers

Early reports: In 1935, 50 years after the start of the use of asbestos in industry, suspicion of an association between asbestosis and lung cancer was reported by Lynch & Smith (1935) in the USA and by Gloyne (1935) in the UK. About 10 years later, case reports of pleural and peritoneal tumours associated with asbestos appeared (Wedler, 1943a,b; Wyers, 1946). Epidemiological proof came from Doll (1955) and Knox et al. (1968), who showed a ten-fold excess risk of lung cancers in those UK asbestos textile workers who had been employed before 1930, when new regulations produced improved dust conditions in factories. Similar findings, but including the development of mesotheliomas, were reported in the USA in 1961 and published later (Mancuso & Coulter, 1963). Possible variations in risk with different types of fibre were rarely considered in the early reports.

Predominant exposure to single types of fibre: In 1956 Wagner started investigating the occurrence of pleural and peritoneal mesotheliomas in the crocidolite mining areas of the North-west Cape Province in South Africa. It was shown that these tumours occurred among men working in the mines, mills, and transportation and handling of the fibre, as well as in the non-mining population living in the vicinity (Wagner et al., 1960). Asbestosis was not invariably present. The latent period between first exposure and tumour development was long - a mean of 40 years. Searches in the other areas in South Africa where amosite and chrysotile had been mined for many years did not reveal these tumours (Sluis-Cremer, 1965). Subsequent surveillance of the mining population in all the asbestos-producing areas in South Africa has added support for a major difference in incidence of the mesotheliomas with the different kinds of asbestos (Harington et al., 1971; Webster, 1973).

Since 1964, following the recommendations of the UICC Working Party on Asbestos Cancers (UICC, 1965), there has been an expansion of epidemiological studies in many parts of the world. A comprehensive

survey by McDonald et al. (1971) of 12,000 workers born between 1891 and 1920 and employed in the chrysotile asbestos mines and mills of Quebec showed that the overall death rate was lower than for Quebec Province as a whole. The lung cancer risk was dose related, and those who had been most heavily exposed to the dust in the past showed about a five-fold increase compared with the least exposed. Of the 2,413 deaths, 97 were due to lung cancer and only 3 to mesotheliomas.

In Finland, anthophyllite mining has also been associated with a small excess bronchial cancer risk, but no mesotheliomas have been reported, despite an intensive search for these tumours and the presence in Finland of an unusually high incidence of pleural thickening and calcification as detected by radiographic and pathological surveys (Kiviluoto, 1960; Meurman, 1966; Meurman et al., 1973). The mining of crocidolite in north-west Australia has been associated with a small number of mesotheliomas (McNulty, 1962).

Exposures to amosite alone in a factory making insulation material were reported by Selikoff et al. (1972, 1973). The increased lung cancer incidence in workers followed up for 20 years or longer was similar to the seven-fold excess seen in a group of insulation workers whose exposures had been to chrysotile and amosite but probably not crocidolite (Selikoff et al., 1970).

Exposures predominantly to mixed types of fibre: In most industrialised countries different types of fibre are mixed during processing, so pure exposures to a single type are rare. Prospective mortality surveys of defined populations of asbestos textile and shipyard workers have provided the most concrete evidence concerning the association between bronchial cancer, pleural and peritoneal mesotheliomas and past exposure to asbestos. Reports came from several countries (Doll, 1955; Mancuso & Coulter, 1963; Selikoff et al., 1964; Elmes & Simpson, 1971; Newhouse, 1969; Bohlig et al., 1970; Kogan et al., 1971; Stumphius, 1971; Rubino et al., 1972). It has also been suggested that other factors such as iron oxide may be contributative (IARC, 1972).

The proportion of the highly exposed groups who eventually die of asbestos-related cancers is still uncertain on account of the very long latent period, the difficulty of establishing population groups exposed earlier than about 1940, and the confounding effect of cigarette smoking. For mesotheliomas - a tumour which occurs rarely except following inhalation of asbestos - the proportion may be about 5% in the higher risk groups.

Newhouse (1969) and Newhouse et al. (1972) have shown that the cancer risk following mixed exposure to chrysotile, amosite and crocidolite is dose related in men and women. Those with low or moderate exposure (as judged by their occupations) showed no excess lung cancer risk; whereas after more than 15 years' follow-up, those with heavy exposures had a six-fold excess among the men and twelve-fold among the women. The occurrence of mesotheliomas was also dose related.

In a naval dockyard population, Harries (1968) showed that while there were no excess cancers associated with asbestos exposure between 1959 and 1968, there has since that time been a steep rise in mesotheliomas. Extensive spraying of crocidolite asbestos was practised between about 1947 and 1955, so that any effects on cancer incidence would be expected to be detectable in the 1970's and onwards.

There is an important enhancement of the risk of lung carcinoma in those exposed to asbestos who also smoke cigarettes (Selikoff et al., 1968; Doll, 1971; Berry et al., 1972; Hammond & Selikoff, 1973). The excess lung carcinoma risk from asbestos in non-smokers is small. In the majority of surveys no link between cigarette smoking and mesotheliomas has been observed (McDonald et al., 1970; McEwen et al., 1970; Selikoff et al., 1970).

Confirmatory evidence of the association between mesotheliomas and past exposure to asbestos comes from many countries where the occupation and residence of case reports of mesothelioma collected in departments of pathology and cancer registers have been investigated.

In some of these studies groups of other lung cancers and other diseases have been included, and information about past occupations was obtained by interviewers who did not know the diseases of those they interviewed (McDonald et al., 1970; McEwan et al., 1970). All these surveys have shown an association between asbestos exposure and mesotheliomas. The more widespread and carefully planned studies have also revealed a proportion of mesotheliomas apparently not related to asbestos. There is still a need to reduce the inter-observer variation in the diagnoses of these rare and pleomorphic tumours (McCaughey & Oldham, 1973). Mesotheliomas are related to the presence and amount of amphiboles in lung tissue as seen by electron-microscopy and other methods (Pooley, 1973).

Non-occupational exposures.: Asbestos fibres and 'bodies' are present in the lungs of most adults who have lived in urban areas (Thomson et al., 1963; Gross et al., 1969; Davis & Gross, 1973; Um, 1971; Oldham, 1973). The total number of fibres in the lungs may be large, but the mass is small (a chrysotile fibre 1 μm in diameter may fragment into 1000 fibrils). There is no evidence at present that this lung burden is a cause of excess morbidity or mortality in the general population. In those occupationally exposed the number of asbestos fibres and bodies is often one, two or more orders greater (Meurman, 1966; Pooley, 1973).

Mesotheliomas have occurred after short exposures to asbestos and in those exposed at home to dusty clothing or to a neighbouring source of asbestos air pollution (Newhouse & Thomson, 1965; Bohlig & Hain, 1973). However, studies of the geographical distribution of cases of mesothelioma in the UK over a 10-year period indicate that the new cases are nearly all from areas where there has been a recognised occupational exposure to asbestos in the past (Gilson, 1970). There is no evidence of an increased incidence of mesotheliomas in the general public as a result of asbestos air pollution.

General considerations: Present evidence is insufficient to indicate what proportion of the variation in cancer incidence in

different parts of the industry - for example, mining and the application of insulation - is attributable to (a) difference in the type of fibre, (b) the difference in past dust exposures or (c) other factors, including technical differences in the surveys. However, the persistently higher incidence of pleural mesotheliomas in the North-west Cape Province crocidolite mining areas as compared with the other mining areas in South Africa, and the firm indication from other widespread sources of a higher risk of these tumours in those exposed to crocidolite, need an explanation. Crocidolite and amosite are similar in chemical composition (See Table 1); their physical differences are possibly more relevant biologically. Timbrell et al. (1971) and Timbrell (1972b) have shown that the crocidolites mined in Cape Province and western Australia have much finer and shorter fibres than do the amosite or crocidolite mined in the Transvaal. This, combined with certain shape factors influencing the aerodynamic properties of the fibres, led them to believe that many more fibres would penetrate to the periphery of the lung in those exposed to the crocidolite dust in Cape Province and Australia than in the Transvaal. Their observations have been supported by aerodynamic studies of the fibres and quantitative experimental animal inhalation work.

The ratio of pleural to peritoneal tumours reported varies widely in different surveys (Elmes & Simpson, 1971). This may be due partly to variations in accuracy of ascertainment. Peritoneal tumours appear to be associated with heavier exposures (Newhouse et al., 1972).

(b) Other cancers

Prospective surveys of the larger defined populations have consistently shown an excess risk of other cancers, especially of the gastrointestinal tract. The excess risk has been less than for lung cancers. The small number of cases and uncertainties in the separation of peritoneal mesotheliomas from other cancers within the abdomen have limited confident interpretation of the evidence

(Mancuso & El Attar, 1967; Elmes & Simpson, 1971; Newhouse, 1973). In chrysotile miners and millers the death rate from intestinal and rectal cancers (ICD 152-154) was related to the intensity of past dust exposure; other abdominal cancers (ICD 155-159) were not (McDonald et al., 1971). In insulation workers an excess of carcinomas of the oesophagus, stomach, colon and rectum was reported (Selikoff et al., 1973). Asbestos-related cancers of the skin are rare despite the frequency of asbestos corns in the skin of workers using the fibre (Alden & Howell, 1944).

4. Comments on Data Reported and Evaluation

4.1 Animal data

Injection of asbestos into the pleural cavity has demonstrated that all major commercial forms can produce mesotheliomas. Experiments suggest that this is probably not due to contaminants such as oils and waxes or heavy metals. It is more likely that the size and shape of the particles are the main factors. Thin, long fibres (less than 0.5 μm diameter and 10 μm in length) seem to be most active in producing tumours. Fine glass fibres of similar diameter can also produce mesotheliomas. The carcinogenicity decreases as the materials are pulverised. Inhalation experiments in rats, guinea-pigs and monkeys can produce fibrotic lesions in the lung and pleura similar to those found in man. By inhalation, mesotheliomas and lung carcinomas have been produced in a small proportion of rats exposed to the four commercial types of asbestos.

4.2 Human data

There is substantial evidence that the risk of lung carcinoma and mesothelioma is small in workers in chrysotile mines and mills, and the same is possibly true for amosite. Some crocidolite mining areas and mills have been associated with a higher risk of mesothelioma. Communities in the neighbourhood of these mines have had, in some instances, an appreciable exposure to asbestos dust. Mesotheliomas have been observed in these populations.

Industrial exposurès to asbestos have usually been to mixed types of

fibre, especially where manufacturing and application are undertaken, for example, textiles, insulation and asbestos cement, and have also occurred in the immediate vicinity. Mesotheliomas have occasionally been diagnosed among families of asbestos workers.

An important excess risk of lung cancer has usually resulted from past heavy exposures. The differences in risk between the several parts of the industry cannot be ascribed to one factor. The type of fibre, past dust levels, the form of dust produced by the process and the length of exposure are all relevant. The risk of lung carcinomas seems to be related to asbestosis.

In manufacturing and application industries mesotheliomas have been caused by exposure to crocidolite, and less frequently to amosite and chrysotile. The period between first exposure and development of tumours is long, usually more than 30 years. The tumours can occur in the absence of other asbestos-related disease.

At the present time, there is no evidence that exposure of the general population to past levels of asbestos dust in the ambient air or in beverages, drinking-water, food or pharmaceutical preparations increased the risk of cancer.

Cigarette smoking enhances the risk of lung carcinoma in asbestos workers to a much greater degree than in the rest of the population.

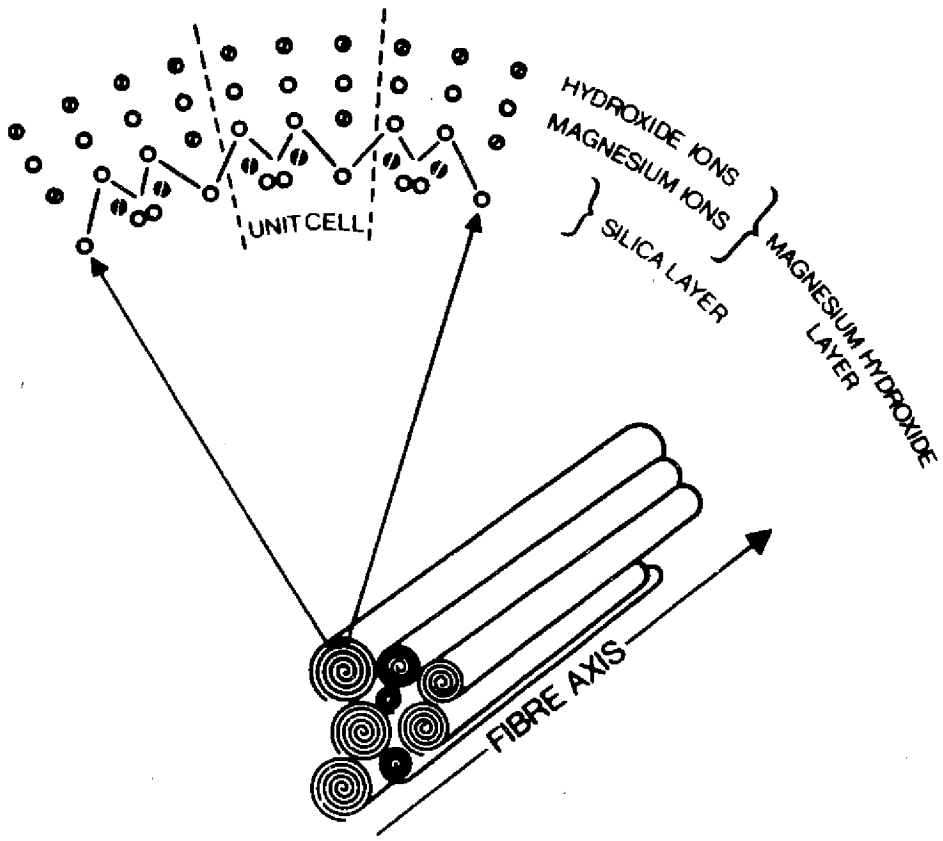

Fig. 1 Schematic diagram of the structure of a chrysotile fibre formed of several scrolls of individual crystallites. Each scroll is formed from a closely connected double layer having magnesium hydroxide units on its external face and silica units on its inner face. The details of a small section of the scroll show the structure of the double layer and of the unit cell based on $Mg_3(Si_2O_5)(OH)_4$.

Figure by permission of Dr A.A. Hodgson.

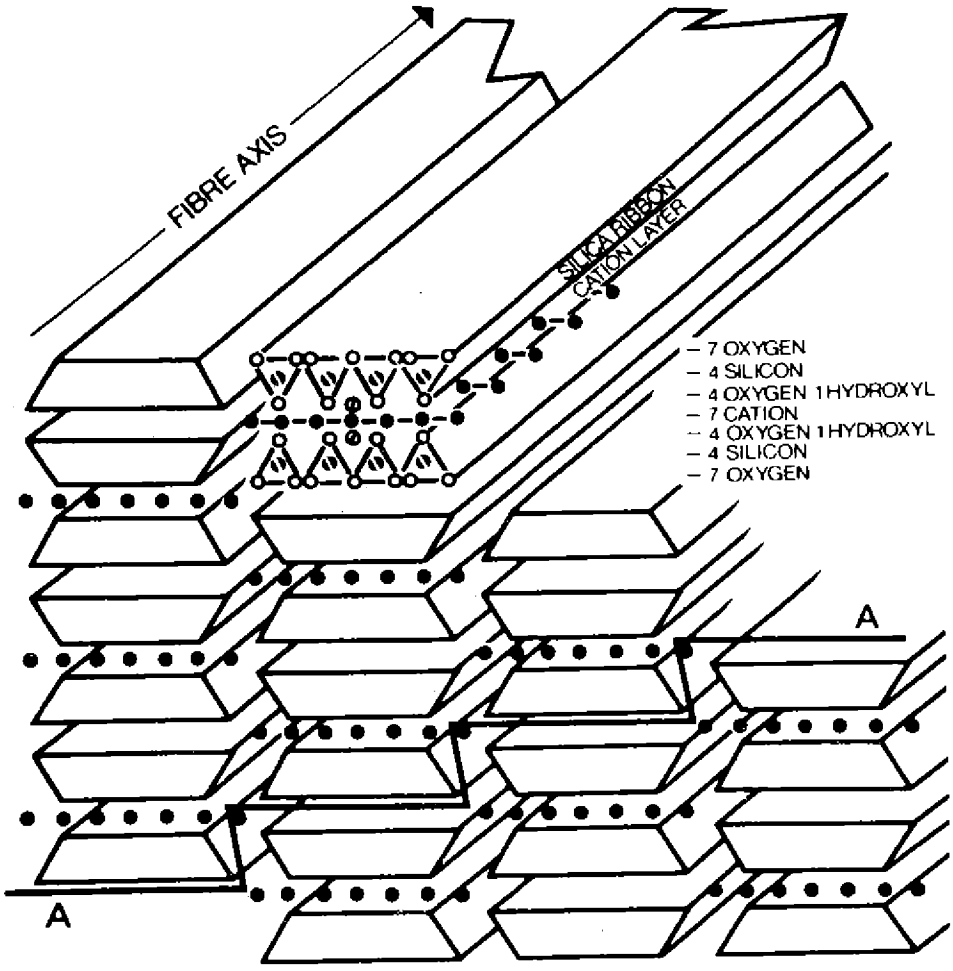

Fig. 2 Schematic diagram of the crystal structure of an amphibole fibre, indicating the unit cell based on $X_7Si_8O_{22}(OH)_2$. The line A-A represents the edge of the preferred cleavage plane along which the fibres will split to form even smaller fibres.

Figure by permission of Dr A.A. Hodgson

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ARSENIC AND INORGANIC ARSENIC COMPOUNDS*

1. Chemical and Physical Data

1.1 Identity

Chemical Name	Formula	Chem. Abstr. No.	Synonyms
Arsenic[1]	As	7440-38-2	None found
Arsenic trioxide [1,2]	As_2O_3	1327-53-3	Arsenic (III) oxide Arsenic sesquioxide Arsenious acid Arsenious oxide Arsenious trioxide Arsenite Arsenolite Arsenous acid Arsenous acid anhydride Arsenous anhydride Arsenous oxide Arsenous oxide anhydride Claudelite Crude arsenic White arsenic
Arsenic pentoxide[2]	As_2O_5	1303-28-2	Arsenic acid anhydride Arsenic oxide Arsenic (V) oxide
Calcium arsenate	$Ca_3(AsO_4)_2$	10103-62-5	Calcium orthoarsenate Tricalcium arsenate
Calcium arsenite	$CaAsO_3H$	27152-57-4	Calcium meta-arsenite Monocalcium arsenite
Potassium arsenate[3]	KH_2AsO_4	7784-41-0	Arsenic acid, monopotassium salt Macquer's salt Potassium acid arsenate Potassium arsenate, monobasic Potassium dihydrogen arsenate

*Considered by the Working Group in Lyon, December 1972

Chemical Name	Formula	Chem. Abstr. No.	Synonyms
Potassium arsenite	$KH(AsO_2)_2.H_2O$[4]	13464-35-2	Arsenious acid, potassium salt Fowler's solution Potassium meta-arsenite
Sodium arsenate	$Na_3AsO_4.12H_2O$[5]	7631-89-2	Sodium ortho-arsenate Arsenic acid, sodium salt
Disodium hydrogen arsenate	$Na_2HAsO_4.7H_2O$[5]	10048-95-0	Arsenic acid, disodium salt heptahydrate Disodium arsenate Sodium acid arsenate Sodium arsenate, dibasic
Sodium arsenite	$NaAsO_2$[4]	7784-46-5	Arsenious acid, sodium salt Sodium meta-arsenite

Footnotes to table:

[1] As_2O_3 is sometimes erroneously called "arsenic".

[2] As_2O_3 is sometimes called "arsenic oxide", but this name is more properly used for As_2O_5. It is relatively common practice for the term arsenic acid to be used for As_2O_5 as well as for the various hydrated products (H_3AsO_4, H_3AsO_3, $H_4As_2O_7$).

[3] The other salts, K_3AsO_4 and K_2HAsO_4, do not appear to be commercial products.

[4] The commercial material has a somewhat variable composition.

[5] The name "sodium arsenate" is applied to both the disodium and the trisodium salts. Because of this confusing use of terms, it is not always possible to determine which substance is under discussion.

1.2 Solubility

The compounds of arsenic considered in this monograph are all soluble in water, although arsenic itself is insoluble. The trioxide and the two calcium salts are of limited solubility. The sodium salts as well as the trioxide are also somewaht soluble in alcohols.

1.3 Stability

The arsenic compounds considered are in many cases not stable and well-defined materials. For example, the arsenites of alkali metals are slowly converted in solution to arsenates by atmospheric oxygen. These same materials in their dry state are said to be decomposed by atmospheric CO_2.

It is strongly recommended that investigators working with these compounds exercise great care to ensure that the material studied is in fact the one reported.

2. Use and Occurrence

(a) Use

Arsenic: Arsenic is produced commercially by reduction of arsenic trioxide with charcoal. Almost all of the 1.07 million pounds of arsenic metal consumed in the United States in 1971 was imported from Sweden, the world's largest producer of arsenic trioxide. An approximate consumption pattern (expressed in million pounds) for the United States in 1971 is as follows: alloying additive, 0.96; electronic devices, 0.08; veterinary medicines, 0.03; total, 1.07 million pounds.

Arsenic pentoxide: Arsenic pentoxide is manufactured commercially by the oxidation of arsenic trioxide with nitric acid followed by the dehydration of the intermedicate crystalline orthoarsenic acid hydrate. It seems likely that total annual US production (exclusive of material used as a non-isolated intermediate) does not exceed 1.25-1.5 million pounds.

It is believed that virtually all of the arsenic pentoxide or arsenic acid that is not used as an intermediate for production of metal arsenates is used as a pre-harvest defoliant (desiccant) for cotton and as an ingredient in formulated wood preservatives, known as Boliden salts.

Arsenic trioxide: Arsenic trioxide is produced commercially as a by-product of metal refining operations. It is present in flue dusts from the roasting of ores, particularly those produced in copper refining. The condensate from this flue dust is termed "crude arsenic" (90-95% arsenic

trioxide). Resubliming produces "white arsenic" (99% arsenic trioxide).

US production of arsenic trioxide in 1968 has been estimated at 7.7 million pounds from domestic ores and 8.5 million pounds from imported ores. Imports were 50.4 million pounds in 1968, but dropped to 32.8 million pounds in 1971.

Major producing countries for arsenic trioxide are Sweden, France, USSR, Mexico and South-West Africa. The consumption pattern for arsenic trioxide in the US in 1968 is believed to have been as follows: pesticides, 77% of total; glass, 18%; industrial inorganic chemicals, 4%; medicine, 1%.

Arsenic trioxide compositions are used as such as an insecticide for dormant application on grapes, in insecticidal dips for goats and sheep, and in combination with mercuric chloride in fungicides for treating fenceposts. By far its biggest use in the pesticide area is in the synthesis of other arsenic-containing pesticides, such as lead, calcium and sodium arsenates, sodium arsenite and arsenic pentoxide.

Arsenic trioxide is widely used as a decolourising additive in the manufacture of nearly all colourless glass, in many coloured glasses, and in certain enamels. Among its uses in the production of industrial inorganic chemicals are purification of synthesis gas and the manufacture of pigments.

Consumption of arsenic trioxide in medicine is believed to be largely by way of arsenic trioxide-based organic arsenicals, although in the past arsenic trioxide itself reportedly has been used in human and veterinary medicine.

Calcium arsenate: Calcium arsenate is probably produced commercially by the reaction of calcium hydroxide with arsenic pentoxide or arsenic acid.

Production of commercial calcium arsenate {70% $Ca_3(AsO_4)_2$} in the US has declined rapidly from a level of 84 million pounds in 1942 to only 0.94 million pounds in 1971.

Historically, calcium arsenate was used mainly as an insecticide, with lesser quantities being used as a herbicide. Although there have been large variations in total consumption from year to year (depending on the extent of the cotton boll-weevil problem), consumption has shown a dramatic downward trend from the high levels of the 1940s. Government restrictions on its use as an insecticide have been a factor in this fall. Consumption had been mainly in boll-weevil control, and also for the control of leaf-eating insects on tobacco and a variety of fruits and vegetables.

The remaining major applications, as of mid-1971, are believed to have been as a herbicide for turf, as a larvicide on poultry droppings for fly control, and on tomatoes for control of hornworms and fruit-worms.

Calcium arsenite: Calcium arsenite is reportedly produced by the reaction of calcium chloride with arsenic trioxide. The amount made in the US is believed to be quite small.

Although calcium arsenite is reported to be useful as a germicide and as an insecticide, it apparently is not registered with US federal agencies for use in these applications. No evidence was found of any present commercial usage.

Lead arsenate: Commercial lead arsenate products are believed to be produced by the reaction of arsenic pentoxide with lead oxide.

Combined production of acid and basic lead arsenate in the US declined rapidly from a level of 90.7 million pounds in 1944 to only 4.16 million pounds in 1970 and increased to 6.17 million pounds in 1971.

It is believed that the major use of lead arsenate occurred first in 1892 as an insecticide against the gypsy moth. It was used against the codling moth (e.g., in apple orchards) and other chewing insects (e.g., cotton boll-weevil) for many years because of its relatively low phytotoxicity, and it apparently found widespread use for insect control on tobacco. Subsequently, it was replaced by synthetic organic insecticides in many of its applications.

As of mid-1971, applications on fruits, particularly apples, were the major use areas; but increasing amounts have been used on grapes in California in recent years.

Lead arsenate was registered in 1971 for use as a growth regulator on grapefruit (to reduce the citric acid content of the juice) and as a herbicide to control crabgrass and other weeds in turf (except around homes).

Potassium arsenate: Production in the US of the synthetic material is believed to be much less than 100 thousand pounds per year.

Apparently, potassium arsenate is not being used commercially at the present time, although it has been reported as being useful in fly baits, for preserving hides, in textile printing and as a laboratory reagent.

Potassium arsenite: Potassium arsenite is reportedly prepared for medicinal uses by the reaction of arsenic trioxide with potassium bicarbonate. Production appears at present to be limited to a very small quantity produced by a few companies specialising in laboratory chemicals and analytical reagents rather than in medicinal chemicals.

Potassium arsenite is available from chemical reagent suppliers in a purified grade. It was formerly available as "Fowler's solution", which was a 1% solution in aqueous ethanol. This solution, which was included in earlier National Formularies, was dropped in 1965. Two older references indicated that Fowler's solution was used as a "hematinic and arsenical". It reportedly was used as a medication for chronic myelogenous leukaemia and in the treatment of certain skin lesions (chronic dermatitis in man). In veterinary medicine, it was reportedly used in the treatment of pulmonary emphysema, chronic coughs, anaemia, general debility, and chronic skin diseases of horses, cattle and dogs. No indication was found that potassium arsenite is presently being used in human medicine. Although an interim tolerance level of 2.7 mg/kg of potassium arsenite was established by the US Environmental Protection Agency in May 1972 from residues in the kidney and liver of cattle and horses (resulting from the external use of potassium arsenite), no

evidence was found that potassium arsenite is presently used on these animals.

Sodium arsenate: Sodium arsenate is probably made commercially by treating arsenic pentoxide or arsenic acid with sodium hydroxide.

In 1968, US annual production was estimated to be slightly more than the imports, which had averaged 304 thousand pounds during the previous five years.

It is believed that the major uses of sodium arsenate are in formulated wood preservatives (known as Wolman salts and Boliden salts) and as an insecticide (in ant killers and animal dips).

Sodium arsenate-based wood preservatives are designed to prevent fungal rot and decay of various wood products (except those intended for food or feed containers).

Sodium arsenate is approved for agricultural use in the US at levels up to 6.0% in bait formulations, for use against ants and for use (at levels of 0.15%) in dips and sprays for goats and sheep.

Sodium arsenate reportedly was formerly used in medicine as an "alterative", as an anthelmintic, and in the treatment of chronic skin diseases.

Sodium arsenite: Sodium arsenite is made by reacting arsenic trioxide with sodium carbonate or sodium hydroxide.

The consumption of sodium arsenite in the US at the present time is undoubtedly much less than the 4.5 million pounds reportedly consumed in 1954. Because of its high mammalian toxicity, sodium arsenite is no longer used as a herbicide along railroad right-of-ways, and governmental restrictions in recent years have limited its present market to certain applications to bare ground, in industrial areas, for tree and stump killing and for bark removal.

It is believed that the major application of this material is still for herbicidal and pesticidal purposes, even though it has been gradually replaced in most of these areas by more efficient organic pesticides with

lower mammalian toxicity. As of mid-1971, its use in the US has been restricted drastically by government regulations.

Preparations containing very low percentages of sodium arsenite are permitted, however, for ant control.

The next most important use of sodium arsenite is as an inhibitor of the corrosion caused in oil well piping when oil wells are acidised with hydrochloric acid. In 1970 it was reported that one million pounds were being used for this purpose in the US. Organic inhibitors were said to be gradually replacing sodium arsenite, however.

Sodium arsenite reportedly is used as an intermediate in the production of (1) arsenic-containing medicinals; (2) arsenical soaps for taxidermists; (3) copper acetoarsenite (Paris Green, a mosquito larvicide); and (4) copper arsenite. No information was found on the quantity consumed for these products or on the other applications mentioned in the literature for sodium arsenite: wood preservation, pigment usage, high preservation and textile dyeing.

(b) Analytical methods

The three main methods for the analysis of arsenic are spark source mass spectrometry, neutron activation and atomic absoprtion. According to Morrison (1972) the detection limits for the first two methods cited are 6×10^{-11}g and 10^{-10}g respectively. The detection limits for atomic absorption vary with the sampling system, the most sensitive being a chemical separation unit coupled with the atomic absorption unit. These units are available commercially, and the Jarrell-Ash Company report detection limits of 10^{-10}g.

Carey (1968) has described a non-instrumental method for the determination of arsenic in organic arsenates.

Care must be exercised in all methods of analysis that arsenic is not lost by volatilisation.

(c) Occurrence

Arsenic:

Natural environment: The occurrence of elemental arsenic in the environment is believed to be very small compared to the amount of arsenic occurring in other forms (usually the pentavalent state). In these forms, arsenic constitutes 7-11% of the gold ores of Sweden and 2-3% of lead and copper ores. It is also found in the ores used in tin smelting, zinc refining and cobalt smelting.

Arsenic is widely distributed in the earth's crust. Water leaching, plant uptake and volcanic activity continue to keep arsenicals widespread in the environment.

Arsenic is present in the phosphate rock used to manufacture fertilizers and detergents.

Tobacco smoke: Arsenic derived from insecticides has been detected in small quantities in tobacco smoke (Holland et al., 1959).

Water: In some parts of the world (e.g., Formosa; Province of Cordoba, Argentina) the levels of inorganic arsenic in water have been found to be higher than elsewhere. In a survey on well water made in 1938 in the Province of Cordoba, Argentina, concentrations of the order of 0.0003% arsenic trioxide and 0.0005% sodium arsenite were found (Arguello et al., 1938).

It has been suggested that fertilizers and detergents manufactured from phosphate rock containing arsenic contribute to the increased arsenic content of river water. For example, in Kansas this was found to be 3-8 µg/kg of arsenic (Angino et al., 1970). The tolerances of arsenic in drinking water given by the US Public Health Service are 10 µg/kg (recommended) and 50 µg/kg (mandatory).

Food: Arsenic can be present in food as a contaminant or as a residue of lead or clacium arsenate used as insecticides, particularly on potatoes and fruit. Arsenic was found in 3.2% samples of food items examined in the US during a market-basket survey; residues ranged between 0.1 and 4.7 mg/kg (Cummings, 1966). The daily intake

of arsenic (as arsenic trioxide) in the same country was calculated to be 0.137-0.330 mg/person (Duggan & Lipscombe, 1969). Other sources indicate that arsenic is present in the diet at levels of 0.05-0.16 mg/kg (referred to wet weight), this corresponding to an intake of 0.15-0.40 mg/person/day (Schroeder & Balassa, 1966; Somers & Smith, 1971).

Arsenic pentoxide: Arsenic pentoxide does not occur as such in nature. Although it may appear in waste streams from where it is produced or used in manufacture, a more probable source of significant quantities is the run-off from cotton fields where it has been used as a defoliant.

Arsenic trioxide: Arsenic trioxide occurs in nature as the mineral arsenolite (As_4O_6). Since arsenic trioxide is formed when arsenic-containing ores are roasted, it may occur as a pollutant in the waste gases and waste waters from ore refineries. Other potential sources include the plants where it is further refined and the many operations in which it is used (pesticide synthesis, glass manufacture, etc.).

Calcium arsenate: Calcium arsenate does not occur in nature as such. It is relatively insoluble, and the presence of excess calcium hydroxide is said to retard its decomposition to water-soluble products. Consequently, it probably would not be readily dissolved in lakes, ponds, streams and ground water supplies. It readily becomes fixed in the soil when used as a pesticide.

Calcium arsenite: Calcium arsenite does not occur as such in nature.

Lead arsenate: Lead arsenate occurs in nature as the mineral shultenite. Since lead arsenate is relatively insoluble in water, it probably would not be readily dissolved in lakes, ponds, streams and ground water supplies. However, lead arsenate does accumulate in the soil. Soils in apple orchards are said to have built up high levels of arsenic as a result of repeated applications of lead arsenate.

Potassium arsenate: Potassium arsenate does not occur as such in nature.

Potassium arsenite: Potassium arsenite does not occur as such in nature.

Sodium arsenate: Sodium arsenate does not occur as such in nature. However, its major applications (wood preservatives and ant killers) probably offer opportunities for sodium arsenate to accumulate in the soil and appear in the run-off from this soil.

Sodium arsenite: Sodium arsenite does not occur as such in nature. It may be present in the run-off from land that has been kept free of vegetation by the use of sodium arsenite as a soil sterilant.

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Man

3.1 Carcinogenicity and related studies in animals

(a) Oral administration

Mouse: No excess of tumours compared with controls was seen in 50 C57BL mice receiving arsenic trioxide in their drinking-water as a 0.0004% solution of 12% aqueous ethanol from the age of two months for 15 months; 28 mice lived for 12 months or more. Higher doses were lethal (Hueper & Payne, 1962). In another study (Baroni et al., 1963), 77 Swiss mice received 0.01% arsenic trioxide in their drinking-water; the tumour incidence in 21 mice surviving 60 weeks was similar to that in controls.

Treatment of Swiss mice with sodium arsenite in their drinking-water at a concentration equivalent to 5 µg arsenic/ml (i.e., an intake more than ten times greater than that of the controls) for their lifespan was associated with a decreased incidence of spontaneous tumours (Kanisawa & Schroeder, 1967) and with no evidence of the induction of other tumours. Thus, 50 tumours at different sites were seen among 140 control mice dying after 15 months of age, whereas the corresponding figure for mice receiving arsenic was 11/71. The decrease was particularly obvious for lung tumours (26 versus 3). The Working Group noted, however, the very low level used in this experiment.

In a brief preliminary report, the oral administration of one drop of an arsenic-containing drug (or Fowler's solution) per week for five months to groups of 30 mice (equivalent to a total dose of 7 mg calculated as As_2O_3) led to a significant increase in the number of tumour-bearing animals. Tumours included adenocarcinomas of the skin, lung and lymph nodes and were observed at 14 months, the time at which the experiment was terminated. No tumours were seen in 15 control mice. Some tumours were also observed in the offspring of the treated mothers, but not in the offspring of the control mice (Knoth, 1966). (This experiment is difficult to interpret due to the briefness of the preliminary report. The follow-up study mentioned was not published.)

Testing of arsenic trioxide for cocarcinogenicity to mouse skin, involving administration of a 0.01% solution as drinking-water for 40-60 weeks in conjunction with treatment with croton oil, DMBA or urethane, gave negative results in 18/77, 37/50 or 28/50 mice surviving the three treatments respectively (Baroni et al., 1963).

Negative results were also obtained with potassium arsenite in tests on cocarcinogenicity to mouse skin (Boutwell, 1963). These involved either oral administration over five days of a total of 2.4 mg potassium arsenite/mouse to 20 Rockland all-purpose mice, two-week feeding of 0.676 g potassium arsenite/kg of diet to 30 skin-tumour-susceptible mice or 48-week feeding of 0.169 g potassium arsenite/kg of diet (0.338 mg/kg of diet in first week only) to 30 skin-tumour-susceptible mice. These potassium arsenite treatments were coupled with skin painting with croton oil or DMBA plus croton oil.

In a controlled study on DBA or BALB/c mice, Milner (1969) showed that 0.01% arsenic trioxide in the drinking-water for 4-13 weeks did not significantly enhance skin carcinogenesis by methylcholanthrene.

Rat: Rats were fed either lead arsenate (10 mg/rat daily) or an equivalent amount of calcium arsenate, and the numbers of survivors at one year were 27 and 51 respectively. Treatment lasted for up to

two years, and no evidence of carcinogenicity was obtained (Fairhall & Miller, 1941).

Treatment of 49 rats for two years with arsenic trioxide either at a constant level of 0.0004% as the drinking-water or of 50 rats at concentrations increasing from 0.0004 to 0.0034% in 12% aqueous ethanol also gave negative results. In the first group 16 rats and in the second group 32 rats survived 22-24 months (Hueper & Payne, 1962).

Byron et al. (1967) reported two-year feeding studies with either sodium arsenite (dietary concentrations corresponding to 0, 15.6, 31.2, 62.5, 125 or 250 ppm arsenic) or sodium arsenate (0, 31.2, 62.5, 125, 250 and 400 ppm arsenic) in groups of 25 Osborne-Mendel rats of each sex. Groups of four to 15 survivors in the treated groups developed no more tumours than did untreated control groups of eight to 12 survivors. At the highest doses the survival rate was reduced.

Ninety-one Long Evans rats of either sex received sodium arsenite in their drinking-water at a concentration of 5 ppm over their lifespan. Tumour incidence was similar to that in untreated controls. On the other hand, 19/91 rats given arsenic developed unspecified "pretumourous lesions" of the liver, whereas such lesions were found in only 10/82 controls (Kanisawa & Schroeder, 1969). The Working Group noted, however, the very low level used in this experiment.

Dog: Eight groups, each of three male and three female dogs, received either sodium arsenite or sodium arsenate in the diet at concentrations corresponding to 5, 25, 50 or 125 ppm arsenic for two years, at which time survivors were killed. No tumours were seen in the limited period of the experiment. In the high level sodium arsenite treatment group, weight loss and early mortality were recorded; six dogs on the highest level died by 19 months and one female on 5 ppm died by three months (Byron et al., 1967).

(b) Skin application

Mouse: Leitch & Kennaway (1922) painted 100 mice three times weekly with a solution of potassium arsenite in alcohol (containing 1.8% arsenious oxide; later reduced to 0.12% due to a high death

rate). Of 33 mice surviving for three months, one developed a metastasizing squamous cell carcinoma after 5.5 months. Neubauer (1947) mentions various unsuccessful attempts to confirm the above finding. More recently, 14 Swiss mice were painted once-weekly for ten weeks with a 1% solution of potassium arsenite in methanol (total dose, 30 mg); and starting 25 days later also received once-weekly applications of 0.17% or 0.085% croton oil in acetone (Salaman & Roe, 1956). Three mice in this group developed skin papillomas, but 4/19 of a control group which received treatment with croton oil alone also developed skin tumours.

Boutwell (1963) also failed to demonstrate a cocarcinogenic effect for potassium arsenite in two groups, each of 20 Rockland all-purpose mice. Testing for tumour initiation involved eight skin paintings of a 0.4% solution in 80% ethanol totalling 1.24 mg/mouse over five days, followed two days later with twice-weekly skin applications of 25 µl of 2% croton oil in benzene. Testing for tumour promotion involved a single application of 75 µg DMBA in 25 µl acetone, followed one week later by twice-daily skin paintings of a 0.4% solution in 80% ethanol, totalling 2.2 mg potassium arsenite/week for 29 weeks.

Baroni et al. (1963) painted 14 female and 54 male Swiss mice with a 1.58% solution of sodium arsenate in water containing a 2.5% solution of Tween 60 or Tween 80 twice-weekly for up to 60 weeks (concentration of arsenic, 0.38%). Two males developed a total of three papillomas, two of which regressed. Sodium arsenate treatment in association with croton oil, DMBA or urethane did not result in a higher tumour incidence, and thus a cocarcinogenic effect for sodium arsenate was not demonstrated.

(c) Subcutaneous and/or intramuscular administration

Mouse: Twenty-four female Swiss mice were given a daily subcutaneous injection of 0.5 mg/kg bw of arsenic as a 0.005% aqueous solution of sodium arsenate throughout pregnancy (a total of 20 injections). Eleven (45.8% of them developed lymphocytic leukaemia or

lymphoma within 24 months from the start of the experiment. By contrast, none of the 20 untreated females which died during the same period developed lymphoma.

Some of the progeny of the arsenate-treated mothers were left untreated, and others were themselves given 20 once-weekly subcutaneous injections of 0.5 mg/kg bw arsenic as aqueous sodium arsenate. All of the animals had been observed for up to 24 months at the time the experiment was reported. Twelve out of 71 untreated progeny and seven out of 97 arsenic-treated progeny were still alive at that time. Thirteen of the 71 untreated progeny developed lymphoma during the observation period, and 41 of the 97 arsenic-treated progeny did so. Both sexes responded similarly, except that none of the arsenic-treated females survived for 24 months. Of the 35 males and 20 females in the untreated controls, 20 and 16 respectively were dead at the time the report was published. Three males developed lymphoma. The age at death in mice with lymphoma was in some instances, but not always, shorter in the As-treated animals than in untreated control males (Osswald & Goerttler, 1971).

(This experiment is difficult to interpret since 20 out of the 55 control animals and some of the experimental animals were still alive at the date of reporting).

(d) Other experimental systems

Intravenous injection: Out of 19 mice (one still alive at the date of reporting), 11 developed lymphoma following 20 weekly i.v. injections of 0.5 mg arsenic (0.005% solution of sodium arsenate) (Osswald & Goerttler, 1971).

Intramedullary injection into the femur: Of 25 Osborne-Mendel rats given about 0.43 mg arsenic as a suspension in lanolin by bilateral injection, 13 survived for over one years, and one developed a sarcoma at the site of the injection. None of six rabbits given a single injection of 0.64 mg arsenic developed a tumour (Hueper, 1954).

Transplacental route: {See sections 3.1 (a) and 3.1 (c)}

3.2 Other relevant biological data

(a) Animals

Following dietary administration of 215 ppm arsenic in the form of calcium arsenate or arsenic trioxide for up to 52 days in rats, highest arsenic levels (146-537 µg/g dry tissue) were found in the kidneys and liver and relatively lower levels in hair, brain, bone, muscle and skin (Morris & Wallace, 1938). Liver and kidney levels of arsenic were greater with calcium arsenate than with arsenic trioxide (Morris & Wallace, 1938).

Arsenate acts as an uncoupler of oxidative phosphorylation and reverses the Crabtree effect (inhibition of cell respiration by excess glucose) in tumour cells (Sauer, 1970). When arsenic trioxide was added to liver homogenates, oxygen consumption decreased (Bencko & Simáne, 1968). Jung & Trachsel (1970) found that arsenic binds to thiol groups of the enzyme DNA polymerase, thus interfering with DNA repair. Rosen (1971) suggested that arsenic can replace phosphorus in the DNA molecule.

(b) Man

Inorganic arsenic is slightly absorbed through the skin when administered in a lipid vehicle, but parenterally-administered arsenic is completely absorbed within 24 hours from i.m. and s.c. sites; 95-99% of the absorbed arsenic is found first in the red cells and then in the kidney and the walls of the gastro-intestinal tract (Oehme, 1972). After two weeks arsenic is stored in the hair, skin and bones (Oehme, 1972). Trivalent arsenic is more toxic than is pentavalent arsenic; the former is converted to the latter, which is rapidly excreted by the kidneys (Schroeder & Balassa, 1966).

At 20 hours after an injection of 4 mg of ^{76}As (sodium arsenite) to a patient with terminal cancer, highest levels of arsenic were found in the liver and kidneys and relatively smaller levels in various other tissues (Ducoff et al., 1948). Also, after an i.v.

injection of labelled sodium arsenite to two human patients either with Hodgkin's disease or lymphatic leukaemia, about 60% of the dose administered was steadily excreted over 6-7 days, predominantly in the urine. Hunter et al. (1942) also found that 33-50% of ^{74}As-labelled potassium arsenite given as four daily s.c. doses each of 1.3> - 1.5 mg to three humans was excreted in the urine within two days of the last dose; <1% of the total dose was excreted in the faeces.

(c) Comparative studies

Following intravenous administration of ^{76}As to five rats, four rabbits and two human patients with Hodgkin's disease and lymphatic leukaemia, the urinary excretion of ^{76}As in the first 48 hours was <10% of the dose in rats, 30% in man and 75% in rabbits (Ducoff et al., 1948). Mice appeared to excrete 75% of an i.p. dose in the first 24 hours. In all species tested the faeces accounted for <10% of the total ^{76}As excreted. Unlike man, rabbit and chicken, the rat retains most of the injected dose in the blood for a prolonged period. Tissue distribution studies revealed highest levels of ^{76}As in the blood and spleen of rats, the liver, kidneys and lungs of rabbits, and the liver, kidneys and spleen of mice and man.

Following daily s.c. doses of ^{74}As-labelled potassium arsenite, Hunter et al. (1942) also observed low blood levels of ^{74}As and relatively higher tissue levels of ^{74}As in rabbits, guinea-pigs, higher apes (two chimpanzees and one baboon) and one human patient with lymphatic leukaemia. In contrast, the rat showed higher arsenic levels in the blood than in the major organs such as liver, kidneys, lungs and spleen. Arsenic did not appear to pass from the blood into the spinal fluid in man, but in apes some passage was evident.

3.3 Observations in man

Several clinical and epidemiological observations have linked certain cancers to heavy exposure to inorganic arsenic compounds.

(a) Arsenic drugs

In the past, inorganic arsenic compounds, particularly Fowler's solution, were widely prescribed for a variety of ailments. It is known that large doses taken internally lead to chronic changes in the skin such as hyperpigmentation and keratoses. The concurrence of chronic skin arsenicism with *in situ* and invasive carcinomas of the skin has been well documented by the large series of Neubauer (1947) and by others (Sommers & McManus, 1953; Sanderson, 1963; Minkowitz, 1964). In 180 patients with skin diseases receiving arsenic-containing preparations, 21 carcinomas of the skin were observed with some dose relationship as to the total dose ingested (Fierz, 1966). Characteristically, the skin cancers are multifocal and often involve unexposed portions of the body and atypical locations such as the palms and soles. Although no epidemiological studies of the cancer risk have been made, the distinctive clinical syndrome resulting from the use of medicinal inorganic arsenic compounds has led to general agreement that the drug can cause skin cancer. Other cancers, notably of the lung (Robson & Jelliffee, 1963) and liver (haemangioendothelioma) (Regelson et al., 1968), have been reported with chronic arsenicism, but the associations in these cases may be only coincidental.

(b) Arsenic in drinking-water

In certain parts of the world (e.g., Reichenstein, Silesia; Cordoba, Argentina) the high levels of arsenic found in drinking-water have been associated with a high rate of arsenicism and skin cancer in the population (reviewed by Neubauer, 1947). Tseng et al. (1968) reported a geographical correlation in Taiwan between levels of arsenic exposure in well-water and the frequencies of skin cancer, hyperpigmentation, keratosis and a peripheral vascular disorder (Blackfoot disease). A clear dose-response relationship was seen between the occurrence of skin lesions, including cancer, and the arsenic content of the water. No excessive occurrence of other cancers has been reported in areas where the water contains arsenic.

Liver haemangioendothelioma was reported recently in one case (Rennke et al., 1971).

(c) Arsenic-exposed occupational groups

(i) Factories

Hill & Faning (1948) examined the proportionate mortality of workers involved in the manufacture of sheep-dip containing inorganic arsenicals who, according to Perry et al. (1948), had substantial dust exposures at levels of arsenic ranging up to 4 mg/m^3. A relative excess of deaths from cancers of the lung and skin was observed among heavily-exposed but not among unexposed workers in the factory. The increases in cancer were ascribed to arsenic compounds.

(ii) Mines and smelters

Snegireff & Lombard (1951) reported that the proportion of deaths from lung cancer among workers exposed to arsenic trioxide in a copper smelter was not significantly different from that of the state-wide male population. However, the mortality experience of former or retired employees was not determined.

Rockstroh (1959) reported 45 cases of lung cancer and two of skin cancer among an unstated number of workers at a nickel refinery. The materials handled were nickel and cobalt ores with a very substantial arsenic content (range 15-50%). The study covered 11 years, with an average work force of 111 men. Among personnel not engaged in production only one case of lung cancer was found. Other agents in the environment included benzpyrene and sulphur dioxide.

Osburn (1957) reported excessive proportionate mortality from cancer of the lung (three times as common) among South Rhodesian miners of gold-bearing ores containing large amounts of arsenic as arsenopyrite. Subsequently, Osburn (1969) re-examined hospital admissions for lung cancer in the gold-mining area and found an additional number of lung cancers; he also found that many miners had palmar hyperkeratosis indicative of chronic arsenicism. A high proportion of the cases were cigarette smokers, suggesting that the high

rate of lung cancer in the area might be due to a combined effect of smoking and arsenical dust exposure.

Pinto & Bennett (1963) studied 229 deaths among copper smelter workers (current and retired) who were exposed to small amounts of arsenic in the copper during the period 1946-60. Arsenic-exposed and unexposed workers were distinguished by types of materials handled and by analyses of air and urine samples. Proportionate mortality figures for the state were applied to the smelter populations; it was concluded that chronic exposure to arsenic as arsenic trioxide in the smelter did not affect the relative frequency of death from respiratory cancer.

Lee & Fraumeni (1969) examined the mortality experience of 8047 men engaged in metal smelting during the period 1938-63. Occupational exposures were categorised into heavy, medium and light for both arsenic trioxide and sulphur dioxide levels. As compared with the male population of the same states, smelter workers had a three-fold excess in mortality from cancer of the respiratory system. This excess was as high as eight-fold for employees who had worked for more than 15 years and who were heavily exposed to arsenic. The risk also increased in proportion to the degree of exposure to arsenic and sulphur dioxide. The results were consistent with the notion that inhaled arsenic is a respiratory carcinogen in man; however, an influence of sulphur dioxide or unidentified agents, whose presence varies concomitantly with arsenic exposure, could not be discounted. When the data were examined by the method of proportionate mortality used in previous studies, the percentage of deaths from respiratory cancer (7.8%) was not significantly different from figures reported for other studies, including those which had been considered as negative (Snegireff & Lombard, 1951; Pinto & Bennett, 1963).

(iii) Vineyards

In the past, certain vineyard workers in Germany and France received heavy exposure to arsenical insecticides, through inhalation of lead arsenate dust and through ingestion of contaminated wine

(Liebegott, 1952; Galy et al., 1963a, b; Latarjet et al., 1964). Clinical reports have documented an association of chronic arsenicism with skin cancer in vineyard workers. The concurrence of arsenicism and lung cancer was observed in post-mortem studies of those vineyard workers who showed cutaneous stigmata or arsenic toxicity at death. Lung cancer occurred in 12 out of 27 men autopsied in one series (Roth, 1957a) and in 9 out of 16 with keratosis in another (Braun, 1958). An excess of liver haemangioendothelioma was suggested in another study (Roth, 1957b).

(d) Arsenic in tobacco smoke

Arsenic derived from insecticides and present in small quantities in tobacco smoke (Holland et al., 1959) has been suspected of influencing the increased risk of lung cancer in smokers (Buechley, 1963). This view is not generally accepted.

4. Comments on Data Reported and Evaluation

4.1 Animal data

Many studies have given essentially negative results, but most of them are not referred to in this monograph because of inadequacies in the experimental design (e.g., too few animals, too short a duration, poor survival, too low a level of exposure).

Adequate oral studies on arsenic trioxide in the mouse and on lead arsenate, calcium arsenate, sodium arsenate, arsenic trioxide and sodium arsenite in the rat gave negative results.

The studies designed to detect cocarcinogenicity to mouse skin by potassium arsenite, sodium arsenate or arsenic trioxide gave negative results.

The two recent preliminary reports suggesting possible carcinogenic effects in mice exposed to sodium arsenate, potassium arsenite and arsenic trioxide by subcutaneous, intravenous, oral and transplacental routes are difficult to interpret on the basis of the findings presented, and the results await confirmation.

4.2 Human data

The available studies point consistently to a causal relationship between skin cancer and heavy exposure to inorganic arsenic in drugs, in drinking-water with a high arsenic content, or in the occupational environment.

The risk of lung cancer is clearly increased in certain smelter workers who inhale high levels of arsenic trioxide. However, the causative role of arsenic is uncertain, since the influence of other constituents of the working atmosphere cannot be determined. An increased relative frequency of deaths from lung cancer has been found in other occupational groups exposed to high levels of inorganic arsenic compounds (e.g., sheep-dip workers, certain mining and vineyard workers).

Cases of lung cancer occurring after the medicinal use of inorganic arsenic compounds, and of liver haemangioendothelioma following various kinds of exposure to arsenic have been reported, but these may be chance associations.

No evidence exists that other forms of cancer occur excessively with heavy arsenic exposure.

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CADMIUM AND INORGANIC CADMIUM COMPOUNDS*

1. Chemical and Physical Data

1.1 Identity

Chemical Name	Formula	Chem. Abstr. No.	Synonyms
Cadmium	Cd	7440-43-9	C.I. No. 77180[1]
Cadmium carbonate	$CdCO_3$	513-78-0	Carbonic acid, cadmium salt (1:1) Otavite
Cadmium chloride	$CdCl_2$	10108-64-2	Cadmium dichloride
Cadmium oxide	CdO	1306-19-0	-
Cadmium sulphate	$CdSO_4$	10124-36-4	Sulphuric acid, cadmium salt (1:1)
Cadmium sulphide	CdS	1306-23-6	Aurora yellow[2] C.I. No. 77199[1] C.I. No. pigment orange 20[1] C.I. No. pigment yellow 37[1] Greenockite

1.2 Solubility

The cadmium compounds considered in this monograph are insoluble in water, except for the chloride and sulphate. The chloride is also soluble in alcohols. The solubility of the metal in tissues and body fluids has been discussed by Weinzierl & Webb (1972).

1.3 Stability

The cadmium compounds considered are stable.

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*Considered by the Working Group in Lyon, December 1972.

[1]Colour Index number.

[2]Does not include pigments where cadmium is part of the name, and trade-name pigments.

2. Use and Occurrence

(a) Use

Cadmium: The world production of cadmium was around 35 million pounds in 1970. The principal sources of cadmium are the sintering of flue dusts and the roasting of zinc ores. Some cadmium metal is also recovered as a by-product of the purification by distillation of slag zinc.

Standard grades of commercial cadmium are usually 99.9% pure. Cadmium sponge is also available for the manufacture of cadmium chemicals, and it typically ranges from 86% to 92% cadmium, with a sizable proportion of the impurity being oxygen (due to the presence of cadmium oxide).

The estimated US consumption patterns (expressed in millions of pounds) for cadmium in all forms (i.e., metal, alloys and compounds) for 1968 and 1971 are as follows: electroplating 7.0, 4.50; plastics stabilizers 2.5, 2.34; pigments (including phosphors) 2.0, 1.26; metal alloys 0.5, -; batteries 0.4, -; others 0.9, -; metal alloys, batteries and others 1.8, 0.90; total 13.3, 9.0.

Cadmium electroplated on metals (primarily steel) is superior to zinc in providing resistance to corrosion.

Nearly all the electroplating is accomplished in baths formulated from cadmium metal and cadmium oxide dissolved in a sodium cyanide solution. These baths consume only an estimated 20% of the total amount of cadmium used in electroplating. Cadmium metal anodes supply the remaining 80%.

The most important applications of electroplating are in automotive and aircraft parts, electronic parts, marine equipment and industrial machinery.

The next largest end use for cadmium is in the production of organo-cadmium compounds which serve as stabilizers for plastics. The most common stabilizers are mixtures of cadmium and barium salts of long-chain fatty acids.

Another use of cadmium is in the preparation of cadmium sulphides, cadmium selenides and mixtures containing these salts for use as pigments (including phosphors). The phosphors require very pure starting materials

and cadmium oxide is preferred as the cadmium source.

Cadmium-containing alloys are used for bearings where the high speeds and temperatures are excessive for tin or lead alloys. Such bearing alloys contain about 99% cadmium in combination with nickel, silver and/or copper. Cadmium alloys used for soldering aluminum contain 10-95% cadmium, with zinc or silver as the other elements. Low-melting alloys of cadmium contain 8-40% cadmium in combination with bismuth, indium, tin and/or lead, and these alloys are used in a variety of applications (e.g., fire-protection fusible links, fusible cores for foundry moulds, holding irregular parts for machining, bending pipes and thin sections, soldering and sealing).

Cadmium is used as the negative electrode in nickel-cadmium storage batteries used in industrial equipment, motor vehicles and many rechargeable household appliances.

Other uses of cadmium that consume minor quantities include alloys for neutron shields and control rods for nuclear reactors.

Cadmium carbonate: Cadmium carbonate can be prepared by absorption of carbon dioxide in cadmium hydroxide solution, and this is believed to be the main commercial process.

Cadmium carbonate is available in a commercial grade having a purity of about 98%. Lead, zinc and iron are present as impurities. Higher purity grades are available for special applications.

The major application is believed to be in fungicides. Cadmium carbonate is used as a lawn and turf fungicide in concentrations of 3.0 and 5.3% as a wettable powder in combination with organic fungicides. The next most significant use is in the preparation of high purity specialty chemicals such as phosphors.

Cadmium chloride: Cadmium chloride is made by dissolving cadmium metal in hydrochloric acid and evaporating to dryness in a stream of hydrogen chloride gas, or by dissolving cadmium oxide or carbonate in hydrochloric acid. The commercial chemical is a mixture of hydrates that approximates to the dihydrate ($CdCl_2.2H_2O$).

The commercial grade of cadmium chloride available in the US typically contains about 51% cadmium and 0.005% each of iron and copper as impurities. There are higher purity grades available for specialised applications such as photographic chemicals and phosphors.

It is believed that pesticides are the largest single use of the commercial grade, and that photographic materials (increasingly) and phosphors are the largest users of higher purity cadmium chloride.

Cadmium chloride is used in non-pasture turf fungicides (cadmium nitrate and cadmium carbonate are used alternatively).

Minor uses for the chloride include its applications in dyeing and calico printing of textiles, the manufacture of thermionic emission coatings for electronic vacuum tubes, as a lubricant ingredient, and in the manufacture of special mirrors.

Cadmium oxide: Cadmium oxide is made commercially by distilling cadmium metal from a graphite retort and allowing the vapour to react with air. The commercial grade of cadmium oxide which is available in the US has a reported purity of 99.7%, with lead and thallium as detectable impurities.

It is generally agreed that electroplating is by far the largest market for cadmium oxide. Total consumption of cadmium in electroplating in the US was estimated at 7 million pounds for 1968 and 4.5 million pounds for 1971. Other important applications are in the manufacture of cadmium electrodes for alkaline storage batteries and in the synthesis of other cadmium salts.

Cadmium sulphate: Cadmium sulphate is made commercially as both the anhydrous ($CdSO_4$) and the hydrated salt ($3CdSo_4.8H_2O$). The usual route for the commercial production of these materials involves dissolving the metal, oxide, carbonate or sulphide in sulphuric acid with subsequent cooling or evaporation to precipitate the salt. Cadmium sulphate is also made as an intermediate in the recovery of cadmium from zinc ore.

Commercial grade cadmium sulphate reportedly contains about 49.5% cadmium (the theoretical cadmium content of $CdSO_4$ is 53.5%).

The principal uses of cadmium sulphate are as an intermediate for plastic stabilizers and in pigments. These uses are estimated to have consumed 3.6 million pounds of cadmium in 1971 in the US.

Cadmium salts of long-chain fatty acids are used as stabilizers for plastics (especially polyvinyl chloride). Cadmium sulphate is used in the manufacture of cadmium sulphide pigments (including phosphors), of cadmium lithopone pigments, and of cadmium sulphoselenide pigments. The use of cadmium sulphate in medicinal preparations has been discontinued because of its toxicity.

Cadmium sulphide: Cadmium sulphide is produced commercially by the reaction of hydrogen sulphide gas with a cadmium salt (mostly cadmium sulphate). It is used mainly in pigments and phosphors that range in colour from yellow to deep maroon.

Because cadmium sulphide and cadmium sulphide-containing materials are used typically for their physical properties rather than for their chemical compositions, the usual measures of product grades are seldom used. Although the commercial grade of cadmium sulphide not otherwise identified as a pigment or a phosphor has a typical content of 98.8% cadmium sulphide and 0.7% cadmium sulphate, most products are much more complex. Thus, cadmium yellow pigments are cadmium sulphide-zinc sulphide mixtures; cadmium lithopone pigments are coprecipitates of cadmium sulphide and barium sulphate; cadmium sulphoselenides are varied mixtures of cadmium sulphide, cadmium selenide and selenium sulphide; and the so-called mercadium pigments contain mercuric sulphide in combination with cadmium sulphide. The cadmium sulphide used in phosphors is usually part of a mixture with zinc sulphide which contains trace amounts of activators such as silver, copper or nickel.

Almost all of the cadmium sulphide produced in the US is used in pigments (including phosphors). These pigments find their principal applications where heat stability (e.g., in coloured vulcanized rubber and some epoxy resins), alkali resistance (printing inks) and resistance to hydrogen sulphide blackening (paints and artists' colours) are needed. Other materials for which cadmium sulphide pigments have been found useful

include glass, ceramics, textiles and paper.

Cadmium sulphide finds its principal phosphor application in cathode ray tube screens. Minor quantities of cadmium sulphide are used in a variety of applications that benefit from the low energy levels required to obtain visible light from this chemical. Phosphorescent tapes and markers, watch and instrument dials, interior decorations, and theatrical black magic are popular uses. X-ray fluorescent screens and body temperature gradient detectors are medical uses.

Cadmium sulphide is the active ingredient in a shampoo designed for use in the treatment of seborrheic dermatitis of the scalp.

(b) Analytical methods

Trace analysis of cadmium may be performed by a number of instrumental methods. The preferred routine technique is atomic absorption spectroscopy, but colorimetry is frequently used due to lower instrumentation cost. A brief survey of techniques is given by Friberg et al. (1971).

(c) Occurrence

Cadmium

Natural environment: Cadmium is a relatively rare element in the earth's crust. Greenockite (CdS) is its most common mineral, and in weathered ores it can be found as otavite ($CdCO_3$). In both forms it is associated with zinc and lead-zinc ores and is recovered as a by-product in the refining of these ores. Trace quantities of cadmium are found also in coals and oils.

Air: Cadmium can enter the air from these natural sources and from a variety of manufacturing operations that involve either cadmium itself (e.g., electroplating for corrosion protection) or zinc that contains cadmium impurity (e.g., galvanizing of steel). Cadmium can enter the atmosphere when cadmium-plated scrap steel is remelted. The production of refined cadmium metal is a potential source of cadmium in the atmosphere (from flue and furnace gases).

In the atmosphere of the working environment cadmium concentrations of 1-3 mg/m^3 (Friberg, 1950) and 0.17-0.46 mg/m^3 (Hardy & Skinner, 1947) have been reported.

Air is not a significant source of cadmium as compared with food. In the general environment it is estimated (World Health Organization, 1972) that the daily intake would amount to 0.02 µg, and even in cities where the levels are 30 times as high this would still be small relative to the food source.

Cigarette smoke: Determinations of cadmium in cigarette tobacco point to a level of 1-2 µg per cigarette. As much as 70% of the cadmium may pass into the smoke phase (Lewis et al., 1972). For a heavy smoker this could add significantly to the daily intake. It is estimated that for each cigarette-pack-year, smokers accumulate through inhalation 0.5 mg cadmium (i.e., about 1.5 µg/day).

Water: Cadmium can enter surface waters from the natural sources described earlier and from a variety of manufacturing operations that involve either cadmium itself (e.g., electroplating for corrosion protection) or zinc that contains a cadmium impurity (e.g., galvanizing of steel). Cadmium can enter the water environment from the plating operations when spent plating solutions are discarded. The production of refined cadmium metal is a potential source of cadmium in nearby surface waters (from ore tailings and washings). Another source of cadmium appearance in surface waters is the application of phosphate fertilizers, since these have been found to contain traces of cadmium. The production of cadmium compounds is not considered a potential source of surface water contamination because of tight process controls in the manufacturing plants.

The general environment level is of the order of 1 µg/l but may be up to 10 µg/l.

Soil: Fertilized soils have been found to contain two to six times the cadmium concentration of adjacent unfertilized land.

Air, water, soil: Virtually all of the cadmium used to stabilize plastics will also enter the environment. If the plastic is incinerated after use the entry will be quite rapid.

The relative significance of some of the above applications in the US was estimated in 1968 by one source[1] and the results are tabulated:

Sources	Quantity processed (Million pounds of cadmium)	Emissions to	Estimated emissions (Thousand pounds of cadmium)
Primary processing sources			
Ore extraction	4.8	Air, Water, soil	0.5 Not available
Ore concentration and metal production	12.8	Air	2100
Conversion of metal to products	13.3	Air	33
Product use	Not available	Air, water, soil	36
Recycle or disposal	-	Air, water soil	2200
Miscellaneous sources			
Fossil fuel combustion	0.7	Air	200-700
Phosphate fertilizer application	0.05	Water, soil	Up to 50
Motor oil use	-	Air, water, soil	1.8

Food: There is little doubt that food is the main source of cadmium intake.

The presence of cadmium in a wide range of both fresh and tinned foodstuffs has been reported by Klein & Wichmann (1945). Schroeder & Balassa (1961) suggest that the main intake in the US diet was from sea

[1] Oak Ridge National Laboratory. Cadmium the dissipated element (ORNL-NSF-EP-21) 1972.

foods and grain products. Vegetables were also a source (Schroeder & Balassa, 1963). In this regard, Klein & Wichmann (1945) found a high cadmium content in tinned oysters; but this was attributed to the tinning solder which had an exceptionally high zinc content. It seems, nevertheless, that cadmium does accumulate in molluscs. A study group in Japan (Yamagata & Shigematsu, 1970) noted a major contribution of cadmium in the Japanese diet from shellfish.

Cadmium carbonate: Cadmium carbonate is found as the mineral otavite, which results from the weathering of cadmium sulphide in ores. Cadmium carbonate might appear in surface waters from the run-off of treated turf. However, it is not as soluble as cadmium chloride, which is also used as a fungicide.

Cadmium chloride: Cadmium chloride does not appear as such in nature, but it can be generated and released into the atmosphere by the incineration of polyvinyl chloride which has been stabilized with organic cadmium salts. Because of its high solubility in water, it may also appear in surface waters from the run-off of treated turf. Discharges from photographic processing may be another source.

Cadmium oxide: Cadmium oxide does not appear as such in nature, but it forms readily from the contact of cadmium vapour with air; thus it is found where cadmium is present in emissions from thermal processes such as ore roasting, pyrosmelting, steel scrap melting, incineration of wastes and burning of fossil fuels.

Cadmium sulphate: Cadmium sulphate does not appear as such in nature. However, it is found in atmospheric emissions from thermal processes involving materials containing cadmium and sulphur. Cadmium sulphate may appear in surface waters near zinc and zinc-lead ore refineries that use sulphuric acid as an ore leachant.

Cadmium sulphide: Cadmium sulphide (greenockite) is the principal mineral in which cadmium occurs, and it is found distributed in small quantities in the zinc, lead and copper ores from whose processing cadmium is a by-product. The sulphide might be found as an atmospheric contaminant in factories where it is employed; but it would probably not be found in

the atmosphere of electronic component plants because there it is generally used in a slurry form. Cadmium sulphide dusts have been reported in working atmospheres. Exposure levels ranged from 18-31 mg Cd/m^3 of air (Princi, 1947).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Man

3.1 Carcinogenicity and related studies in animals

There are three reviews on the biological action of cadmium (Flick et al, 1971; Friberg et al., 1971; World Health Organization, 1972) and two general reviews on metal carcinogenesis which include cadmium (Furst & Haro, 1969; Sunderman, 1971).

(a) Oral administration

Mouse: Schroeder et al. (1964) observed no more tumours in 48 males and 39 females given 5 ppm cadmium acetate in their drinking-water for life than in 44 male and 60 female controls. The mean survival was 814 days in the treated groups and 957 days in the control group. The Working Group noted that the experimental level used, which was designed to simulate the human exposure level, was too low for carcinogenic evaluation.

Rat: Kanisawa & Schroeder (1969) gave 47 rats cadmium acetate at a concentration of 5 ppm in their drinking water for life. The tumour incidence was comparable in test rats to that in 34 controls. Schroeder et al. (1965) also found a similar tumour incidence between 50 males and 46 females given 5 ppm cadmium acetate in their drinking-water for life and 42 male and 44 female controls. About 50% of test and control animals survived 24-33 months. The Working Group noted that the experimental level used, which was designed to simulate the human exposure level, was too low for carcinogenic evaluation.

(b) Inhalation and/or intratracheal administration

Rat: The studies on cadmium oxide and cadmium chloride fumes extended over too limited a period for any conclusions to be drawn

on the reported absence of tumours (Paterson, 1947).

(c) Subcutaneous and/or intramuscular administration

Mouse: Of 20 male stock mice given 11 once-weekly s.c. injections of 0.05 mg cadmium sulphate in water, six survived up to 20 months. None developed tumours at the injection site, and the incidence of neoplasms at other sites did not exceed that in a control group. However, testicular atrophy and moderate interstitial-cell hyperplasia was observed in the six animals surviving after 20 months (Haddow et al., 1964; Roe et al., 1964).

Gunn et al. (1963) found that a single s.c. injection of 0.03 mmole/kg bw of cadmium chloride in 26 Charles River mice damaged the testicular vascular supply. The tissue regenerated, but 14 months later 17% of the mice had interstitial-cell tumours. No local tumours developed in 25 mice receiving the same dose of cadmium chloride plus 3 mmoles/kg bw of zinc acetate (Gunn et al., 1963). No tumours developed in 25 controls. Survival data in treated and control groups were not given.

Rat: Of 20 male albino rats given ten once-weekly s.c. injections of 0.5 mg cadmium sulphate in water, 14 developed sarcomas at the site of injection within 20 months of the start of treatment. All showed testicular atrophy and many showed interstitial-cell hyperplasia. Of 18 rats examined post-mortem within 20 months of the start of treatment 10 had interstitial-cell tumours. Castration changes were observed in the pituitaries. All treated animals were dead by 20 months. No interstitial-cell tumours were seen in 15 controls that survived up to 18 months (Haddow et al., 1964; Roe et al., 1964). Similar results were obtained with cadmium-precipitated rat ferritin (Haddow et al., 1964; Roe et al., 1964), but no local tumours were induced by cadmium-free ferritin (Roe et al., 1968). Repeated once-weekly s.c. injections to rats of 0.05, 0.1 or 0.2 mg cadmium sulphate (0.016-0.64 mg cadmium) for two years failed to produce neoplastic changes in the prostate gland (Levy et al., 1973).

A single s.c. injection of 0.03 mmole/kg bw of cadmium chloride induced spindle-cell sarcomas at the injection site in 6/45 rats (Knorre, 1970a, b) and interstitial-cell tumours in 10/25 rats observed up to two years (Knorre, 1971). Sarcomas developed between 7 and 18 months after injection and interstitial-cell tumours after 355 days. Skin atrophy, ulceration and local necroses were noted just after administration of the agent. No interstitial-cell tumours or local sarcomas developed in 32 controls observed for 706 days.

Gunn et al. (1963) found that a single s.c. injection of 0.03 mmole/kg bw of cadmium chloride in 25 Wistar rats caused testicular vascular damage. The tissue regenerated, and after 11 months 68% of the rats had interstitial-cell tumours. In 20 controls no interstitial-cell tumours developed. Of 17 rats receiving cadmium chloride plus zinc acetate, only 2 developed tumours at the site of injection after 11 months.

Gunn et al. (1964) reported that after a single s.c. injection of 0.03 mmole/kg bw of cadmium chloride 9/22 rats developed injection-site sarcomas and 19/22 developed interstitital-cell tumours of the testes after 10 months. Zinc acetate, given as three s.c. doses of 1 mmole/kg bw, inhibited the development of both types of tumours induced by cadmium chloride, the resulting tumour incidence being 2/17 for sarcomas and 3/17 for interstitial-cell tumours. No interstitial-cell tumours or local sarcomas developed in 18 controls.

Gunn et al. (1967) showed that four s.c. doses of 0.17 mg of cadmium chloride produced pleomorphic sarcomas at the injection site in 3/30 male Wistar rats 12-16 months later.

A single s.c. injection of 25 mg cadmium sulphide into 15 female Wistar rats elicited an acute inflammatory reaction by 24 hours and extensive fibrosis at the injection site by three months (Kazantzis & Hanbury, 1966). In another experiment, a single s.c. injection of 50 mg cadmium sulphide into ten female Wistar rats produced small,

hard, mobile nodules at the injection site, and in 6/10 rats the nodules developed into sarcomas by ten months post-injection. All animals died or were killed by one year (Kazantzis, 1963; Kazantzis & Hanbury, 1966). A more intense inflammatory reaction with ulceration of the overlying skin followed a single s.c. injection of 50 mg cadmium oxide into ten female rats, and 8/10 animals developed tumours at the injection site within one year post-injection. No local tumours developed in ten controls given a s.c. injection of the vehicle, physiological saline (Kazantzis & Hanbury, 1966).

Lucis et al. (1972) gave rats a single s.c. injection of 0.02-0.03 mmole/kg bw of cadmium chloride. Interstitial-cell tumours developed in 13/15 rats before 11 months, and two rats developed fibrosarcomas at the injection site.

When 11 rats received injections of 0.34 mg cadmium chloride into four different sites on the same day (s.c., i.m., subperiosteal and into the liver or kidney, and salivary gland or ventral prostate), tumours developed at two s.c., one i.m. and one subperiosteal mesenchymal mesodermal sites by about ten months post-injection (Gunn et al., 1967).

Heath & Daniel (1964) produced malignant tumours at the injection site in 9/10 and 6/8 rats given i.m. injections of 14 and 28 mg cadmium powder, respectively. The last animals without tumours were killed at 84 weeks. A high proportion of these tumours were rhabdomyosarcomas, but some were fibrosarcomas. In general, the tumours were fairly well differentiated, but many metastasized. These findings were confirmed by Heath & Webb (1967).

Of 14 rats given a 50 mg i.m. dose of cadmium sulphide, 5 developed tumours from 9 to 15 months after injection (Kazantzis & Hanbury, 1966).

Zinc powder failed to inhibit cadmium powder tumorigenesis when both compounds were given i.m. to two groups of 25 male and 25 female Fischer rats. Either two injections of 5 mg cadmium powder or one of 3 mg cadmium powder plus 12 of 5 mg zinc powder were given at monthly

intervals. By one year, 12 females and 14 males in the cadmium group and 8 females and 14 males in the cadmium plus zinc group developed fibrosarcomas (Furst & Cassetta, 1972).

3.2 Other relevant biological data

(a) Animals

In mammals (including man) cadmium is virtually absent at birth, but it will accumulate especially in the liver and kidneys over a life-time (Schroeder & Balassa, 1961; Schroeder et al., 1964).

Harrison et al. (1947) exposed dogs to cadmium chloride mists in a chamber. They found a LC_{90} of 0.32 mg cadmium/l of air for a 30-minute exposure. Death in all instances was due primarily to pulmonary injury, but tissue analysis showed that much of the cadmium chloride leaves the lungs and is distributed throughout the body. The highest concentrations were found in the kidneys.

Studies in mice using aerosols of cadmium compounds showed that particles of less than 2 μ were found in the lungs and were also absorbed and concentrated in the kidneys. Cadmium sulphide was the exception; it remained in the lungs (Potts et al., 1950).

In many species, including mice, rats, guinea-pigs, rabbits, dogs and monkeys, about 10-40% of cadmium is retained after inhalation of cadmium compounds. The amounts retained differ with different compounds (Potts et al., 1950; Barrett et al., 1947).

^{115}Cadmium was found to accumulate selectively in the rat kidney cortex (Gunn & Gould, 1957). ^{109}Cadmium given s.c. to rats immediately appeared in the blood plasma and then disappeared rapidly; after six days only 2% of the dose was excreted in the faeces (Lucis et al., 1969). In female mice the biological half-time of a single injection of ^{109}Cadmium was estimated as 200 days (Richmond et al., 1966).

Studies in mice indicate that less than 10% of an oral dose is absorbed (Richmond et al., 1966; Suzuki et al., 1969). Calcium deficiency increases the tissue retention of cadmium in the rat (Larsson & Piscator, 1971).

In rabbits given 60 daily s.c. injections of cadmium sulphate, only about 1% of the dose was excreted in the urine (Friberg, 1952). In goats, dogs and rabbits given i.v. or s.c. injections, only a small percentage of the absorbed cadmium is excreted via the faeces (Miller et al., 1968; Burch & Walsh, 1959; Axelsson & Piscator, 1966).

Metallothionein has been found in the liver of cadmium-exposed mice and rabbits (Nordberg et al., 1971a, 1972), in the red blood cells and plasma of mice (Nordberg et al., 1971b) and in the duodenal mucosa of several species (Starcher, 1969; Evans et al., 1970). This low molecular weight protein is thought to play an important role in the transport of cadmium in the body. A high single dose of cadmium partly bound to metallothionein had no effect on the testes, while the effect on the kidneys was more pronounced. This may be explained by the fact that the cadmium-metallothionein is filtered through the glomuleri and reabsorbed by the tubules of the kidney (Nordberg, 1971).

Johnson et al. (1970) gave rats and domestic fowls s.c. injections of ^{109}Cd chloride and examined certain tissues at 5-40 minutes post-injection. Approximately 10% of the total ^{109}Cd was found in the liver, 50% in muscle and 30% in the testes. Pretreatment with zinc or selenium reduced the amount of ^{109}Cd in the testes and muscles. If subcellular location is indicative, the domestic fowls and the rats pretreated with zinc and selenium appear to have different defence mechanisms against cadmium. Cadmium chloride administered to rats by s.c. injection or directly into the liver is transported to the testes (Lucis et al., 1972).

Barrett et al. (1947) reported the LD_{50} of inhaled, arc-produced cadmium oxide fumes in various species as follows: mice, under 700 mg/m^3; rats, 500 mg/m^3; guinea-pigs, about 3500 mg/m^3; rabbits, about 2500 mg/m^3; dogs, about 4000 mg/m^3; monkeys, 15,000 mg/m^3. Exposures ranged from 10-30 minutes. They found that the retention of the cadmium oxide by the animals' lungs was constant and amounted on average to 11%. Some cadmium was found in other organs, but it

appeared to have originated from the ingestion of cadmium trapped in the upper respiratory tract.

Rabbits given one to eight s.c. injections of 9-18 mg/kg bw of cadmium chloride showed destruction of testicular cells (spermatogenic and interstitial) within 5-21 days. There was also hyperaemia and interstitial haemorrhage. The kidneys, spleen and liver were also affected (Cameron & Foster, 1963).

In rabbits repeated s.c. injections of 0.25 mg/kg bw of cadmium chloride on five days per week for 11-29 weeks produced renal lesions, characterised by degenerative cytoplasmic and nuclear changes in the proximal tubular epithelium. The lesions increased in severity and seemed to descend along the nephrons in a way directly proportional to the exposure time. Cadmium deposits were found in the kidneys of all exposed rabbits. In rabbits exposed for 24 weeks and killed after a further 30 weeks degenerative changes were slight and signs of tubular epithelial regeneration were evident (Axelsson et al., 1968). Proteinurea was noted, characterised by a low urinary albumin and an increase in α_2-, β- and γ- globulins (Axelsson & Piscator, 1966). Doses of 0.65 mg/kg bw of cadmium sulphate given s.c. six days per week produced similar results (Dalham & Friberg, 1957).

Schlaepfer (1971) showed that after a single s.c. dose of cadmium chloride (10 mg/kg bw) in rats, some endothelial cells underwent progressive degeneration. This was associated with an increase of vascular permeability of horseradish perioxidase.

(b) Man

The hazard from cadmium exposure may extend to the general population, and persons not exposed to cadmium in their work may inhale or ingest cadmium to produce toxic effects (Kendry & Roe, 1969).

Excretion via the faeces of normal humans is about 30-50 µg/day (Essing et al., 1969; Tipton & Stewart, 1970; Tsuchiya, 1969). The retention of ingested cadmium varied between 4.7-7% in five adult men (Rahola et al., 1971).

Only a very small proportion of the daily absorbed dose will be excreted, and this amount depends on how recent the exposure has been and on the total body burden. Normal urinary excretion in humans amounts to about 1-2 µg per day (Imbus et al., 1963; Lehnert et al., 1968); on occupational exposure, this level is not raised significantly (Tsuchiya, 1967, 1969).

The slow excretion results in a very long biological half-life for absorbed cadmium, which has been estimated to be 16-33 years (Kjellström et al., 1971; Tsuchiya & Sugita, 1971).

About half of the total body burden is found in the liver and the kidneys (Smith et al., 1960). The cadmium in these organs is mainly bound to a low molecular weight protein, in the form of a metallothionein (Friberg et al., 1971).

Schroeder & Balassa (1961) found that cadmium appears to accumulate in the human kidney with age up to the sixth decade. At present, mean levels of cadmium in the renal cortex of adults vary from 30 to 80 µg/g according to country (Schroeder & Balassa, 1961; Ishizaki et al., 1970; Kitamura et al., 1970).

It has been calculated that a daily intake of 62 µg would be necessary to reach 50 µg/g wet weight in the renal cortex at age 50, assuming an absorption rate of 5%, and that 10% of the daily absorbed dose is rapidly excreted and also that 0.005% of the total body burden is excreted daily (World Health Organization, 1972). A similar calculation, assuming that 0.01% of the total body burden is excreted daily, showed that the daily intake would have to be 88 µg to reach the same final level in the renal cortex (Kjellström et al., 1971).

Morgan (1969) observed wide variations in the levels of cadmium in the kidneys and liver of 25 patients with cancer.

Morgan (1970, 1971) subsequently observed a significant increase in renal hepatic and blood cadmium concentrations in patients with bronchogenic carcinoma, a significant increase in the hepatic cadmium

concentration in patients with emphysema and a significant increase in renal and hepatic cadmium concentrations in patients with emphysema plus bronchogenic carcinoma. This author, however, discounted the possibility that cadmium was responsible for these diseases.

Inhalation leads to the retention in the tissues of large amounts of cadmium, particularly in the kidneys, liver, pancreas and thyroid (Friberg, 1957). Barrett et al. (1947) calculated the lethal inhalation dose of cadmium oxide in man to be 2500 mg/m^3 for a one-minute exposure.

Cases of chronic cadmium poisoning have been described in working atmospheres containing 1-3 mg/m^3 (Friberg, 1950) and 0.17-0.46 mg/m^3 (Hardy & Skinner, 1947). However, no evidence of cadmium poisoning was obtained in workers occupationally exposed to 1.0-31 mg/m^3 of cadmium sulphide dust (Princi, 1947).

Proteinurea was seen after prolonged cadmium exposure in man (Potts, 1965; Holden, 1969; Piscator, 1962).

In two fatal cases of acute exposure to cadmium oxide, haemorrhages were seen in the lung alveoli (Paterson, 1947).

3.3 Observations in man

Two reports have indicated a possible relationship between heavy occupational exposure to cadmium and prostate cancer. Potts (1965) reported a survey of 74 men exposed for ten or more years to high levels of cadmium oxide dust in the production of alkaline batteries. Of the eight deaths in this group, three were from prostate cancer and two from other forms of cancer. Kipling & Waterhouse (1967) reported preliminary results of an epidemiological study of 248 workers with a previous history of at least one year's exposure to cadmium oxide. Prostate cancer was diagnosed in four cases, significantly more than the 0.58 case expected on the basis of incidence rates derived from the regional cancer registry in Birmingham. Three out of these four cases are those referred to earlier by Potts

(1965)[1]. Subsequently, no excess of any form of cancer has been detected in three studies of men occupationally exposed to cadmium, but the sample size of each study was small (Humperdinck, 1968; Holden, 1969; Friberg et al., 1971).

Winkelstein & Kantor (1969) reported a geographical correlation between the frequency of prostate cancer and the amount of suspended particulate air pollution in various communities. The authors suggested that cadmium exposure might be involved in the association, but measurements of this agent in the atmosphere were not made.

4. Comments on Data Reported and Evaluation

4.1 Animal data

Single or repeated s.c. injections of several inorganic cadmium compounds (cadmium chloride, sulphate, sulphide and oxide) result in the development of injection-site sarcomas in the rat. Local tumours were also produced in rats by i.m. injection of cadmium powder and cadmium sulphide.

Interstitial-cell tumours of the testis were found in rats and mice given s.c. injections of soluble cadmium salts (cadmium sulphate and cadmium chloride). The testicular tumours in both species were of interstitial-cell origin and were only seen following testicular atrophy. The pituitary glands of these animals showed castration changes. It is likely, therefore, that the testicular tumours developed as a result of an indirect action of cadmium on the testis. Repeated s.c. injections of cadmium sulphate in the rat failed to produce neoplastic changes in the prostate gland.

The negative results obtained when cadmium acetate was administered orally to rats and mice are not acceptable as evidence of the non-carcinogenicity of this compound since only one low dose level was used.

No conclusions could be drawn from the negative findings obtained in inhalation studies on rats with cadmium oxide and cadmium chloride fumes because of the short duration of the experiments.

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[1] Personal communication from Dr M.D. Kipling

4.2 Human data

Two studies suggest that occupational exposure to cadmium oxide may increase the risk of prostate cancer in man, but the size of the groups examined was too small to allow definite conclusions to be drawn.

No data are available to suggest that non-occupational exposure to cadmium constitutes a carcinogenic hazard.

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CHROMIUM AND INORGANIC CHROMIUM COMPOUNDS*

1. Chemical and Physical Data

1.1 Identity and solubility

Chemical name	Formula	Chem. Abstr. No.	Aqueous solubility	Synonyms
Chromium	Cr	7440-47-3	Insoluble	-
Calcium chromate	$CaCrO_4$	10060-08-9	Slightly soluble	Chromic acid (H_2CrO_4), calcium salt (1 : 1) Calcium chromate (VI) Calcium chrome yellow C.I. No.77223[1] C.I. pigment yellow 33[1] Gelbin yellow ultramarine Pigment yellow 33 Steinbühl yellow
Chromic oxide	Cr_2O_3	1308-38-9	Insoluble	Anadomis green Casalis green Chrome green (hydrated) Chrome ochre Chrome oxide Chromia Chromic oxide green Chromium oxide Chromium (III) oxide Chromium oxide green Chromium oxide pigment Chromium sesquioxide C.I. No.77288 and 77278[1] 11661 Green[1] Green chrome oxide Green chromium oxide Green cinnabar Green oxide of chromium Green oxide of chromium OC-31 Green rouge Guignet's green (hydrated chromic oxide)

* Considered by the Working Group in Lyon, December 1972

Chemical name	Formula	Chem. Abstr. No.	Aqueous solubility	Synonyms
				Leaf green Levanox green GA Oil green Oxide of chromium Pure chromium oxide green 59[1] Ultramarine green
Chromium dioxide	CrO_2	12018-01-8	Insoluble	Chromium (IV) oxide
Chromium trioxide	CrO_3	1333-82-0	Soluble	Chromic acid Chromic (VI) acid Chromic anhydride Chromic trioxide Chromium oxide
Lead chromate	$PbCrO_4$	7758-97-6	Insoluble	Canary chrome yellow 40-225P Chrome lemon Chrome yellow C.I. No.77600[1] Chromic acid (H_2CrO_4), lead (II) salt (1 : 1) C.I. Pigment Yellow 34[1] Cologne yellow C.P. Chrome yellow light C.P. Chrome yellow medium C.P. Chrome yellow primrose King's yellow Lead chromate (VI) Leipzig yellow Lemon yellow Paris yellow Plumbous chromate
Potassium dichromate	$K_2Cr_2O_7$	7778-50-9	Soluble	Dichromic acid dipotassium salt Potassium bichromate Potassium dichromate (VI) Red potassium chromate

[1] Colour Index number.

Chemical name	Formula	Chem. Abstr. No.	Aqueous solubility	Synonyms
Sodium dichromate	$Na_2Cr_2O_7$	10588-01-9	Soluble	Dichromic acid disodium salt Sodium bichromate Sodium dichromate (VI)

The following compounds were included in the monograph but no information on "Use and Occurrence" is available:-

Barium chromate	$BaCrO_4$	10294-40-3	Insoluble	Chromic acid, barium salt C.I. No. 77103[1] C.I. pigment yellow 31[1] Baryta yellow Lemon yellow Permanent yellow Steinbühl yellow Ultramarine yellow
Chromium acetate	$Cr(COOCH_3)_3.H_2O$	1066-30-4	Soluble	Acetic acid, chromium(III) salt
Chromium carbonate	$Cr_2O_3.xCO_2.4H_2O$	6449-00-9	Slightly soluble	Carbonic acid, chromium(III) salt
Chromium phosphate	$CrPO_4$	7789-04-0	Insoluble	Phosphoric acid, chromium(III) salt
Potassium chromate	K_2CrO_4	7789-00-6	Soluble	Natural potassium chromate Chromic acid, dipotassium salt
Sodium chromate	Na_2CrO_4	7775-11-3	Soluble	Chromic acid, disodium salt
Strontium chromate	$SrCrO_4$	7789-06-2	Slightly soluble	Chromic acid, strontium salt
Zinc chromate hydroxide	$Zn_2CrO_4(OH)_2.H_2O$	12206-12-1	Slightly soluble	Zinc yellow Buttercup yellow

[1]Colour Index number.

The compounds considered in this monograph are essentially insoluble in organic solvents with the single exception of chromium trioxide which is soluble in alcohol and ether. In aqueous systems the solubilities of the chromium salts vary greatly even within families of related materials (see Table).

1.2 Stability

The compounds of chromium considered are all stable materials,although those having water of hydration may be expected to gain or lose water as a function of temperature.

Both chromium trioxide and sodium and potassium dichromate are powerful oxidizing agents and should be handled with care.

2. Use and Occurrence

(a) Use

Chromium: The metal is made commercially in the US by two processes: (1) an electrolytic method in which a chromium-containing electrolyte (prepared by dissolving a high carbon ferrochromium in a solution of sulphuric acid and chromium potassium sulphate) is subjected to electrolysis; (2) an aluminothermic reduction method in which chromic oxide is reduced with finely divided aluminium. Chromium metal is available in the US as electrolytic chromium (99.5% Cr), aluminothermic chromium (98.5% Cr) and ductile chromium (99.99% Cr).

In 1970, US production of chromium metal and metal alloys other than ferrochromium alloys was reported to have been 31 million pounds (about 75% was made by the electrolytic method). This included production of chromium briquets, exothermic chromium additives and miscellaneous chromium alloys, in addition to chromium metal.

Chromium metal and metal alloys other than ferrochromium alloys are used primarily in stainless and heat-resisting steel and alloy steel.

They are used in alloys to impart strength, hardness and resistance to corrosion, oxidation, wear and heat.

Calcium chromate: Calcium chromate is produced commercially by the reaction of calcium chloride with sodium chromate. Hydrated forms can be made, but the anhydrous salt is the only product of commercial significance. It is believed that calcium chromate is largely used as a corrosion inhibitor and as a depolarizer in batteries.

The use of calcium chromate in protective coatings for steel and light metals is sometimes reported as a pigment use, but the primary function of calcium chromate in these products is that of a corrosion inhibitor.

Chromic oxide: The anhydrous material is produced industrially by heating chromic hydroxide, by heating dry ammonium dichromate, or by heating sodium dichromate with sulphur and washing out the sodium sulphate. The hydrated material is made commercially by calcining sodium dichromate with boric acid and hydrolysing the resulting chromium borate. Both the anhydrous and hydrated oxide could be present in products which have been coloured green by their addition.

US production of the most important type of chromic oxide, chromic oxide green, was reported to be about 13.2 million pounds in 1971.

The major portion of chromic oxide (anhydrous and hydrated) is used as a pigment. A substantial portion is also used in metallurgy and, to a lesser extent, as a catalyst, in refractory brick, and as a chemical intermediate.

Anhydrous chromic oxide is the most stable green pigment known and is used in applications requiring heat, light and chemical resistance (e.g., in glass and ceramics). It is used in dyeing polymers, and its resistance to alkalis makes it a valuable colorant for latex paints. It finds special use in colouring Portland cement, in green granules for asphalt roofing and in camouflage paints.

Metallurgical grade anhydrous chromic oxide is used in the manufacture of chromium metal and aluminium-chromium master alloys. It is used as a catalyst in the preparation of methanol, butadiene and high density polyethylene. In refractory brick, chromic oxide is used as a minor component to improve performance.

Hydrated chromic oxide is also used as a green pigment, especially for automotive finishes.

Chromium dioxide: Chromium dioxide is made by the thermal decomposition of chromium trioxide, but it is not sold on the open market since apparently the only use is in high-energy magnetic tapes. The tapes are reported to give improved fidelity at lower speeds than conventional magnetic tapes based on acicular ferric oxide. At present, the amount of chromium dioxide used in these tapes is probably only a few million pounds, but consumption may increase in the future.

Chromium trioxide: Chromium trioxide is produced industrially by the reaction of sodium dichromate with sulphuric acid.

Its major use is in chromium plating, particularly in the production of automobiles. Additional uses in other metal-finishing operations include aluminium anodizing, which has been used extensively on military aircraft assemblies; chemical conversion coatings, which provide both decorative and corrosion protection effects; and the production of phosphate films on galvanised iron or steel. Important non-plating uses of chromium trioxide include use as a corrosion inhibitor for ferrous alloys in recirculating water systems, as an oxidant in organic synthesis, and in catalyst manufacture. Small amounts of chromium trioxide are also used to modify the properties of basic magnesite refractories.

Lead chromate: Lead chromate can be produced by reacting sodium chromate with lead nitrate, or by reacting lead monoxide with chromic acid solution. Details of various commercial procedures for the manufacture of lead chromates are not generally revealed by the producers. By varying the proportion of the reactants, either lead chromate ($PbCrO_4$) or basic lead chromate ($PbO.PbCrO_4$) can be produced. High lead chromate content is associated with the more yellow pigments, while increasing the basic lead chromate content gives orange and red pigments.

Production data for lead chromate are not available, however it is undoubtedly produced by the pigments industries of most industrialised countries. The combined production of chrome yellow and chrome orange is reported for the US, however, and amounted to 64.9 million pounds in 1970.

To prevent lead poisoning in small children who eat chips of peeling paint from old housing, the US Environmental Protection Agency has ordered a ban on interstate shipments of paints for domestic use containing more than 0.06% lead, effective from 31 December 1973. This ban will undoubtedly significantly reduce the US consumption of lead chromate pigments and will thereby reduce whatever contribution lead chromate presently makes to lead and chromium pollution problems.

Potassium dichromate: Potassium dichromate is produced industrially by roasting chrome ore with potassium carbonate, or preferably by reacting sodium dichromate with potassium chloride.

Combined production of potassium dichromate and potassium chromate in 1966 was estimated at 6-8 million pounds, with the potassium dichromate believed to be the more important chemical industrially.

Potassium dichromate was once the leading chromium compound, but it has been largely replaced in many applications by sodium dichromate. The present market for potassium dichromate appears to consist of a large number of small volume applications. Probably the largest uses are photomechanical processing, chrome pigment production and wood preservative formulations.

Sodium dichromate: Sodium dichromate is produced industrially by the reaction of sulphuric acid on sodium chromate, which is obtained by calcining a mixture of chromite ore (a chromium iron oxide), limestone and soda ash.

Since sodium dichromate is the primary chrome chemical from which all of the others are made, it could occur as a water pollutant from chrome chemicals plants or in losses during pigment production or leather tanning operations. However, in the US, maximum permissible chromium concentration standards have been set for hexavalent chromium ion which have resulted in fairly widespread adoption of recycling and conservation practices.

Combined US production of hydrated sodium dichromate and hydrated sodium chromate was 276.4 million pounds in 1971. Sodium dichromate is

the principal commercial product and is preferred to the more expensive sodium chromate.

Consumption of sodium dichromate is believed to be largely in chrome pigments production, chromium trioxide production, and in leather tanning and industrial water treatment.

Chrome pigments are used in paints, printing inks, for colouring paper, rubber, linoleum, composition floor tile, and in practically all other applications for coloured pigments.

The second largest usage for sodium dichromate is in the production of chromium trioxide (see the discussion of chromium trioxide for more information).

(b) Analytical methods

Many methods have been used to determine chromium. At present the three most sensitive methods are: gas chromatography (Taylor, 1971; Sievers et al., 1967); spark source mass spectroscopy (Evans & Morrison, 1968); and graphite furnace atomic absorption method (Kahn, 1972). Conventional methods for the atomic absorption determination of chromium are described by Feldman et al. (1967) and Moten (1970). Iida & Fuwa (1967) used a multichannel flame spectrometer. The detection limits for the four methods are 10^{-14} g, 5×10^{-11} g, 10^{-11} g and 10^{-9} g respectively. Gas chromatography has been successfully employed by Savory et al. (1969); gas chromatography-mass spectometry by Wolf et al. (1972); chemiluminescence by Seitz et al. (1972); and X-ray spectrochemistry by Gofman (1962). Gorsuch (1962) has shown that dry ashing of organic samples results in little loss of chromium; however, low-temperature ashing is preferable. Livingston & Wacker (1971) have summarised methods for metal decontamination of chemicals and lab ware. Cellular analysis for chromium may be accomplished by ion microscope or laser microprobe techniques. Neutron activation analysis is adapted for sub-nanogram detection (Coleman et al., 1967).

(c) Occurrence

Chromium

Natural environment: Chromium is found in nature only in the combined state and not as the element. It is derived mainly from chromite ($FeO.Cr_2O_3$), which is found in considerable quantities in Rhodesia, Russia, South Africa, New Caledonia and the Philippines and contains 40-50% chromium (Bidstrup & Case, 1956).

Air: Falk (1970) found a chromium content of 15 ng/m^3 in the particulate of air samples taken in the US in 1964 and 1965. Generally, the concentration in air is between 0.002 and 0.02 $\mu g/m^3$. Stocks (1960) found 0.9-21.5 ng/m^3 in 23 localities in Northern England and Wales in 1956-58.

Water: In the sea, the concentration is less than 1 µg/kg, but annually, 6.7×10^6 kg of chromium are added to the oceans (Bowen, 1966). In the rivers, the concentration lies between one and ten µg/kg. The permissible level of Cr^{6+} in drinking-water is 50 µg/kg (WHO, 1963).

Soil: Chromium is present in the soil at levels which vary from traces to 250 mg/kg as chromic oxide (Robinson, 1914), and particularly in soils derived from basalt or serpentine (Bowen, 1966).

Food: Chromium is present in low concentrations in most foods (Morgan, 1972).

Calcium chromate: Calcium chromate does not occur naturally. There is a possibility that it may occur in wastes associated with its production or use.

Chromic oxide: Chromic oxide and hydrated chromic oxide do not occur in nature.

Chromium dioxide: Chromium dioxide does not occur in nature.

Chromium trioxide: Chromium trioxide does not occur in nature. It may occur as a water pollutant in the effluent from chrome chemicals plants. It may also occur as a polluting effluent from chrome-plating

and other metal-treating shops. However, maximum permissible chromium concentration standards have been set in the US for hexavalent chromium which have resulted in fairly widespread adoption of recycling and conservation practices.

Lead chromate: Lead chromate occurs in nature as the minerals crocoite and phoenicochroite. Because lead chromate is insoluble in water, it seems unlikely that it occurs in significant quantities in the waste streams from plants producing or using it.

Potassium dichromate: Potassium dichromate does not occur in nature.

Sodium dichromate: Sodium dichromate does not occur in nature.

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Man

3.1 Carcinogenicity and related studies in animals

(a) Oral administration

Mouse: Groups of 54 male and 54 female Swiss mice receiving 5 ppm chromic acetate in the drinking-water for life did not show more tumours than control mice (Schroeder et al., 1964). No difference was found in the survival of the females compared to the controls, but treated males died 100 days earlier than control males (831 versus 957 days), with 60% of the males surviving 18 months. The very low experimental level used was designed to simulate the level of human exposure.

Rat: A level of 5 ppm chromic acetate given in the drinking-water until death did not significantly increase the incidence of tumours arising at various sites in rats of either sex as compared with controls (total numbers of tumours: 16/39 in treated males; 18/35 in treated females; 9/35 in control males; 15/35 in control females) (Schroeder et al., 1965). At least 60% of the animals survived for up to two years. Treated females lived as long as control females, but treated males lived up to 100 days longer than control males. The very low experimental level used was designed to simulate the level of human exposure.

(b) Inhalation and/or intratracheal administration

Mouse: The following mice were exposed four hours per day, five days per week to a mixed chromate dust in dust chambers containing 1-2 mg/m^3 of soluble chromium until they died or were killed (total dose of chromium inhaled, 480-1205 mg-hours): 127 Swiss females for up to 55 weeks; 10 Swiss males for up to 39 weeks; 34 strain A females for 16 weeks; 45 strain A females for 24 weeks; 110 strain A females for 35 weeks and 52 strain A males for 46 weeks; 50 C57BL males and 61 C57BL females for up to 42 weeks. No squamous cell carcinomas were produced, and the incidence of lung adenomas did not significantly exceed that in control mice in any strain. The experiment lasted for up to 101 weeks (Baetjer et al., 1959b).

Nettesheim et al. (1971) exposed by inhalation 136 C57BL/6 mice of each sex to calcium chromate dust over their lifespan and found twice as many pulmonary adenomas in males and four times as many in females as in controls; no squamous cell carcinomas appeared in these two experiments.

Baetjer el al. (1959b) gave five to six intratracheal instillations of a mixed chromate dust equivalent to 0.04 mg chromic trioxide, either to 20 Swiss males which were then observed for 32 weeks, to 45 and 110 Swiss females observed for up to 32 and 48 weeks respectively, to 28 and 77 strain A females observed for up to 31 and 52 weeks respectively, to 17 strain A males observed for up to 52 weeks or to 48 C57BL males and 47 C57BL females observed for up to 32 weeks. Experimental animals developed no more lung tumours than did untreated control animals. Steffee & Baetjer (1965) gave six intratracheal injections at six-week intervals of 0.03 ml of a 0.2% saline suspension of basic potassium zinc chromate to 62 strain A mice and observed them until death. No bronchogenic carcinomas were found, only alveologenic adenomas in 50% of the test animals and 44% in 18 control animals.

Rat: Steffee & Baetjer (1965) exposed 78 Wistar rats by inhalation to a mixed chromate dust with an average of 49 mg-hours of chromic trioxide per week (3-4 mg/m^3 chromic trioxide) over their

lifespan and gave 16 once-monthly intratracheal injections of 0.1 ml of a suspension consisting of 0.5% mixed roasted chromate dust plus 0.6% potassium dichromate equivalent to 0.07 mg chromium/dose to 38 Sherman rats. They did not observe any significant difference in tumour incidence between experimental and control groups. Rats survived for 16 or more months.

Laskin et al. (1970) implanted calcium chromate (unspecified dose) by an intrabronchial pellet technique and found six squamous cell carinomas of the bronchus in 100 rats (details of strain and sex not given) observed for up to 136 weeks. Chromic chromate, chromic oxide and chromic trioxide did not give any tumours of the lungs in three groups each of 100 rats observed for up to 136 weeks.

Rabbit: No lung tumours were found by Steffee & Baetjer (1965) in eight rabbits exposed on four days per week for up to 50 months to a mixed chromate dust by inhalation or in ten rabbits exposed to similar material by intratracheal injection. Similar studies with zinc chromate in seven rabbits and lead chromate in seven rabbits also gave negative results.

Guinea-pig: Of 50 guinea-pigs exposed by inhalation to a dust containing a mixture of potassium dichromate-sodium chromate (with an average of 3-4 mg/m^3 chromic oxide), three developed alveologenic adenomas. Nineteen were given six once-monthly intratracheal instillations of mixed chromium material containing 12-14% soluble chromium compounds, 19 were given six one-monthly intratracheal instillations of a pulverised residue dust from which the sodium chromate had been leached, 21 were given six once-monthly intratracheal instillations of zinc chromate and 13 animals were given six once-monthly intratracheal instillations of lead chromate. All the animals were observed until they died (no further details are given). None developed carcinomas of the lungs (Steffee & Baetjer, 1965).

(c) Subcutaneous and/or intramuscular administration

Mouse: Payne (1960a) injected s.c. 10 mg of sintered calcium chromate in tricaprylin (trioctanoin) into 26 male and 26 female C57BL

mice, 18 of which survived for 12 months. No tumours were seen. A similar injection with sintered chromium trioxide (29 survivors at 12 months) resulted in no tumours. With calcium chromate (nine survivors at 12 months) one sarcoma developed at the site of s.c. injection. A single s.c. injection of chromite ore (equivalent to 0.5 mg chromium) gave rise to sarcomas at the site of injection in three out of 52 C57BL mice (at least 46 survivors at 15 months), while chromic phosphate (single injection of 2.64 mg as chromium) gave no tumours in 52 C57BL mice (44 survivors at 15 months) (Payne, 1960b).

Rat: When 39 rats (20 males, 19 females) were given 16 i.m. injections of 2 mg sodium dichromate in gelatin and observed for two years (17 alive at 18 months) no tumours appeared at the injection site (Hueper & Payne, 1962).

Heath et al. (1971) produced sarcomas after 17 months in 74 female Strangeways rats at the site of i.m. injection with 28 mg wear particles from prostheses made from a cobalt-chromium alloy (26.9% chromium, 65.3% cobalt, 6.11% molybdenum and 0.36% manganese) suspended in horse serum.

Roe & Carter (1969) injected rats once-weekly i.m. for 20 weeks with calcium chromate in arachis oil (total dose 19 mg). Of 24 rats, 18 developed invasive spindle cell and pleomorphic cell sarcomas at the injection site, none of which metastasized. The mean time of tumour appearance was 323 days (duration of experiment, 440 days). No tumours developed in a control group given arachis oil only.

(d) Other experimental systems

Intravenous injection: According to Hueper (1955) 25 C57BL mice received six once-weekly injections of 0.05 ml of a 0.005% suspension of chromium in gelatin-saline. Six animals survived 12 months but none survived 18 months. No tumours were observed.

Of 25 male Wistar rats given six once-weekly injections of 0.18 ml of a 0.05% suspension of powdered chromium in gelatin-saline, 15 survived one year (Hueper, 1955). The tumour incidence and type were comparable with those of controls.

Hueper (1955) gave six once-weekly injections of 0.5 ml/kg bw of a 5% suspension of powdered chromium in gelatin-saline to eight rabbits followed by the same course of treatment four months later; four rabbits injected with the vehicle alone served as controls. A further six female rabbits received six once-weekly injections of 5 ml of a 5% suspension of chromite ore in gelatin-saline, and the treatment was repeated in 4/6 rabbits nine months later. In the former group 3/8 survived three years and in the latter group 6/6 died or were killed within four years. No tumours were observed during these periods in test or in control animals.

Intramuscular implantation: Payne (1960a) observed nine implantation-site sarcomas in 24 C57BL mice which survived over 12 months after implantation of 10 mg sintered calcium chromate in sheep fat, and one sarcoma in 25 mice which survived more than 12 months after i.m. implantation of 10 mg calcium chromate in sheep fat. The groups initially contained 26 males and 26 females in each of these tests; no local tumours developed in 20 controls surviving more than 12 months.

Payne (1960b) reported that none out of 52 C57BL mice implanted i.m. with 10 mg roasted chromite ore (equivalent to 0.79 mg chromium) developed tumours at the implantation site. Details of survival are not given, but at least one mouse lived for 22 months.

Hueper (1958) implanted small cubes composed of 25 mg chromite roast ores suspended in 75 mg sheep fat into 31 female rats and found three sarcomas at the site of implantation after 24 months. No implantation-site tumours occurred in the controls. Similar experiments by Hueper & Payne (1959) also produced sarcomas at the implantation site after one year in 8/35 rats given implanted pellets of 25 mg calcium chromate in 50 mg sheep fat and in 15/35 rats given implanted pellets of 25 mg sintered chromic trioxide in 50 mg sheep fat. No implantation-site tumours were obtained with either the insoluble barium chromate (25 mg in 75 mg sheep fat) in 35 rats or in 35 controls. Implantation of 25 mg chromic acetate in a gelatin capsule in 35 rats produced one local sarcoma after 24 months (Hueper & Payne,

1962).

Payne (1960a) implanted a gelatin capsule containing 12.5 mg calcium chromate into rats and found local sarcomas in 2/4 rats that survived for 12 months or more. Of 35 rats given an implant of 25 mg roasted chromite ore (2 mg as chromium), one developed a sarcoma at the implantation site after 22 months (Payne, 1960b).

Hueper (1961) tested other compounds by i.m. implantation and found the following incidence of implantation-site sarcomas after 27 months in groups of 22-34 rats: chromic chromate, 24/33 (16 alive at one year); calcium chromate, 9/32 (22 alive at one year); strontium chromate, 15/33 (20 alive at one year); barium chromate, 0/34 (30 alive at one year); lead chromate, 1/33 (28 alive at one year); sodium dichromate, 0/33 (25 alive at one year); zinc chromate hydroxide, 16/34 (22 alive at one year); chromium acetate, 1/34 (30 alive at one year). None of the 35 control rats given implants of sheep fat alone developed local tumours.

Intrapleural administration: After 14 months no significant tumours were seen in 50 C57BL mice receiving six injections of 0.2 ml of a 0.005% suspension of chromium in gelatin-saline every other week; 32 mice survived 7-14 months (Hueper, 1955). When 30 male and 25 female A mice were given four injections of 0.05 ml of a 2 or 4% suspension of mixed chromium dust in olive oil at 4-6 week intervals they did not show more lung tumours during an observation period of 38 weeks than a control group of 18 males and 23 females observed for 101 weeks (Baetjer et al., 1959b).

Following six once-monthly injections of 0.05 ml of a 33.6% suspension of powdered chromium in lanolin into 17 female and eight male Osborne-Mendel rats, haemangiomas appeared in three females within 24 months (Hueper, 1955). Following six once-weekly injections of 0.1 ml of a 0.5% suspension of powdered chromium in gelatin-saline into 25 male Wistar rats no tumours appeared within 30 months (Hueper, 1955).

Hueper & Payne (1962) found that sodium dichromate gave rise to one adenocarcinoma of the lung after 16 injections of 2 mg into 20 male and 19 female Bethesda Black rats observed for up to two years. After intrapleural implantation of 12.5 mg of calcium chromate in a gelatin capsule to 14 rats, eight developed malignant tumours (not specified) at the site of implantation after two years; but no tumours occurred after two years at the site of eight intrapleural implantations over 13 months of 25 mg chromic acetate in gelatin capsules to rats.

Other compounds tested in rats by Hueper (1961) in experiments lasting 27 months gave the following number of tumours at the site of intrapleural injection (details of dose and tumour type not given): chromic chromate, 26/34 (15 alive at one year); calcium chromate, 20/32 (0 alive at one year); strontium chromate, 17/28 (nine alive at one year); barium chromate, 1/31 (30 alive at one year); lead chromate, 3/34 (32 alive at one year); sodium dichromate, 0/26 (20 alive at one year); zinc chromate hydroxide, 22/33 (11 alive at one year); chromic acetate, 3/34 (18 alive at 15 months). None of the 34 control rats showed tumours.

Of 14 male and 11 female Osborne-Mendel rats receiving six once-monthly injections of 0.05 ml of a 73.4% suspension of chromite ore in lanolin, 13 survived one year. One thoracic tumour (fibrosarcoma) was found after 24 months (Hueper, 1955).

Hueper (1958) implanted 75 mg sheep-fat cubes containing 25 mg chromite roast ore into the pleural cavity of 25 male Bethesda Black rats and observed squamous cell carcinoma of the lungs in 2/4 rats that survived 19-24 months. Only 4/15 controls survived this period. A lung adenoma appeared in 1/15 controls given an implant of sheep fat only. In a similar experiment, 25 mg roasted chromite ore in 50 mg sheep fat were implanted intrapleurally into 15 male and 20 female Bethesda Black rats (i.e., 2 mg as chromium) and produced implantation-site tumours (unspecified) in three rats over 17 months. No tumours were seen in 35 rats injected intrapleurally with the sheep-

fat vehicle only (Payne, 1960b).

Intramedullary administration into the femur: Following injection of 0.2 ml of a 50% (by weight) suspension of powdered chromium in lanolin to 25 male Wistar rats, 14 survived one year, and one spindle-cell sarcoma resulted after 24 months (Hueper, 1955). Of 15 male and 10 female Osborne-Mendel rats injected with 0.05 ml of a 50% suspension containing 58 mg chromite ore in lanolin, 15 survived one year, but no tumours developed at the injection site (Hueper, 1955).

3.2 Other relevant biological data

(a) Animals

Chromium is an essential element, acting as a cofactor in glucose metabolism and in other enzyme systems (Mertz, 1969). This author also gives a detailed review of the metabolism of trivalent chromium.

Potassium dichromate, administered intratracheally to guinea-pigs, is rapidly absorbed and is found in the spleen and in increased concentrations in the red blood cells. Trivalent chromium binds to lung tissue more readily than does hexavalent chromium (Baetjer et al., 1959a). Grogan (1957) found that chromite dust is easily translocated from the lungs of rabbits or dogs to other organs, and chromium appears in increased amounts in the urine. Brain and muscle appear to have little affinity for injected chromium, but there is a considerable uptake by bone (Visek et al., 1953).

Water-soluble chromates disappear rapidly from the lungs into the circulation and other organs after intratracheal administration, whereas trivalent chromic chloride does not (Baetjer et al., 1959a). When it is injected intravenously into rats sodium chromate accumulates rapidly in the kidneys and later in the spleen (Kovalchuk, 1966).

The absorption of chromium from the digestive tract has been studied in cats by Akatsuka & Fairhall (1934), who concluded that at least for chromic carbonate or phosphate no absorption occurs.

Similar results were obtained in rats by Aronson & Rogerson (1972), who used an EDTA complex of trivalent chromium. Brard (1935) found that chromates are absorbed from the digestive tract or from the site of s.c. administration. Trivalent chromium is not absorbed from the latter route.

Trivalent chromium is transported in rat serum bound to siderophilin, albumin, γ-globulin and two α-proteins (Rebière, 1964; Jett et al., 1968).

Gray & Sterling (1950) postulated that hexavalent chromium is reduced enzymically to trivalent chromium which is then bound to a haemoglobin. On the other hand, hexavalent chromium is bound to erythrocyte globin (Kovalchuk, 1966).

It is possible that pH plays a role in the physiological distribution of hexa- and trivalent chromium; the latter precipitates at physiological pH and forms chromic hydroxide. Trivalent chromium may also precipitate with proteins. Baetjer (1956) summarises the work.

Skin may also reduce hexavalent to trivalent chromium, which may then bind to proteins (Samitz & Katz, 1963). The sulphydryl groups are involved in the binding of trivalent chromium, whereas hexavalent chromium does not bind at all (Samitz & Katz, 1964). Cr^{6+} penetrates cell membranes while Cr^{3+} does not (Grogan, 1957, 1958). Grogan (1958) administered hexavalent chromium i.v. into hens and found chromium in the leucocytes and erythrocytes. Both tri- and hexavalent chromium bind to egg albumin (Grogan & Oppenheimer, 1955).

Chromium has been found in all ribonucleic acids, regardless of the original source (Wacker & Vallee, 1959).

Champy-Hatem (1962) and Hatem & Champy (1960) believe that imidazoles form complexes with chromium and that a histamine-trivalent chromium complex may be related to cancer induction.

(b) Man

Chromium is poorly absorbed from the human gastro-intestinal tract (Schroeder et al., 1962). The daily excretion is 63-78 μg/day

in the faeces and 100-160 µg/day in the urine for a dietary intake of 200-290 µg/day (Tipton & Stewart, 1970).

Hepatic concentration of chromium is high in childhood and declines to very low levels after the age of 20 years (Schroeder et al., 1962).

Human tissues contain 20 to several hundred µg/kg of chromium; chromium in biological material is in the trivalent state (Mertz, 1969).

3.3 Observations in man

Clinical observations from Germany in the 1930s raised the suspicion that workers in chromate plants were prone to lung cancer (reviewed by Baetjer, 1950a). Machle & Gregorius (1948) demonstrated a high relative frequency of death from respiratory cancer among workers in the chromate-producing industry. Among 193 deaths from all causes at six chromate-producing plants in the US, 21.8% resulted from respiratory cancer, as compared to an expected frequency of 1.4% in a control group from other industries. In a study of medical records from two hospitals near a chromate-producing plant, Baetjer (1950b) found that the proportion of chromate workers among lung-cancer patients was significantly higher than among other hospital groups. Mancuso & Hueper (1951) reported that among 33 deaths from all causes in men working for at least one year at a chromate plant in Ohio, 18.2% were attributed to respiratory cancer, as contrasted with an expected frequency of 1.2% for the male population in the county where the plant was located. Brinton et al. (1952) reported excess mortality from lung cancer in a survey of workers at several chromate-producing plants in the US. There were 26 deaths from lung cancer, compared with 0.9 deaths expected on the basis of the mortality experience of the US male population. The risk of other forms of cancer among chromate workers did not exceed expectation.

Subsequently, Bidstrup & Case (1956) reported significantly high lung-cancer mortality in a follow-up survey of men at three British chromate factories. Twelve deaths were found, as compared with three expected on the basis of national death rates. The investigators

evaluated the possibility that the increased risk of lung cancer among the workers may be related to diagnostic bias, place of residence, social class or smoking; however, these explanations were discarded in favour of an occupational carcinogen. For other cancer sites, the observed and expected numbers of deaths were similar.

Nasal-sinus and otopharyngeal cancers have been described in chromate workers (Spannagel, 1953), but there is no evidence that the risk of these neoplasms exceeds expectation.

The available studies clearly indicate a high risk of lung cancer in the US and Great Britain. In addition, clinical observations from Germany have suggested a possible relation of lung cancer to the chrome pigment industry (Gross & Kölsch, 1943; Letterer et al., 1944). The risk of respiratory cancer is not higher among chromite-ore miners but seems to be increased only in workers involved in the production and processing of chromium compounds. There is no consensus on the specific chromium compounds that are carcinogenic in man, although monochromates were implicated in one study (Machle & Gregorius, 1948).

4. Comments on Data Reported and Evaluation

4.1 Animal data

In many experiments, various chromium compounds have been shown to induce tumours in mice and rats. Calcium chromate has been found to be carcinogenic by several routes of administration, producing epithelial tumours of the lung by intrabronchial implantation and sarcomas by intramuscular and intrapleural administration to rats.

Of the other chromium salts tested in the rat by intramuscular and intrapleural administration, chromic chromate and zinc chromate hydroxide were highly evocative of sarcomas at the site of injection in the rat, whilst barium chromate, lead chromate, chromic acetate and sodium dichromate were inactive or practically inactive. Strontium chromate was tested only by intramuscular implantation and evoked many local sarcomas.

Studies involving oral administration of chromic acetate in mice and rats which gave negative results were considered inadequate because the

level of exposure was low.

4.2 Human data

There is an excessive risk of lung cancer among workers in the chromate-producing industry. It is likely that exposure to one or more chromium compounds is responsible, but the identity of this or these is not known.

There is no evidence that non-occupational exposure to chromium constitutes a cancer hazard.

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NICKEL AND INORGANIC NICKEL COMPOUNDS*

1. Chemical and Physical Data

1.1 Identity

Chemical Name	Formula	Chem. Abstr. No.	Synonyms
Nickel	Ni	7440-02-0	Carbonyl nickel powder C.I. No.77775[1]
Nickel acetate tetrahydrate	$Ni(COOCH_3)_2.4H_2O$	6018-89-9	Acetic acid, nickel (II) salt Nickelous acetate tetrahydrate
Nickel acetate, anhydrous	$Ni(COOCH_3)_2$	373-02-4	Acetic acid, nickel (II) salt Nickelous acetate
Nickel carbonate, basic	$2NiCO_3.3Ni(OH)_2.4H_2O$		None found
	$NiCO_3.2Ni(OH)_2.4H_2O$	1271-28-9	Zaratite
Nickel carbonate	$NiCO_3$	3333-67-3	Carbonic acid, nickel (II) salt C.I. No.77779[1] Nickelous carbonate
Nickel carbonyl	$Ni(CO)_4$	13463-39-3	Nickel tetracarbonyl
Nickelocene	$(C_5H_5)_2Ni$	1271-28-9	Di-π-cyclopentadienylnickel
Nickel oxide	NiO	1313-99-1	Green nickel oxide Nickel monoxide Nickel (II) oxide Nickelous oxide Nickel protoxide
Nickel subsulphide	Ni_3S_2	12035-72-2	Nickel sulphide[2] Heazlewoodite

*Considered by the Working Group in Lyon, December 1972

[1]Colour Index number

[2]There is a monosulphide of nickel (NiS) and there is considerable confusion in the published literature between these two substances.

Nickel sulphate	$NiSO_4$	7786-81-4	Nickelous sulphate Sulphuric acid, nickel (II) salt
Nickel sulphate hexahydrate	$NiSO_4.6H_2O$	10101-97-0	Blue salt Nickelous sulphate hexahydrate Single nickel salt Sulphuric acid, nickel (II) salt, hexahydrate

1.2 Solubility

The nickel compounds considered in this monograph are in general insoluble in water, except for the acetate and sulphate. Both nickel carbonyl and nickelocene are soluble in a variety of organic solvents such as alcohol, benzene, chloroform and acetone. The solubility of metallic nickel in tissue and body fluids has been discussed by Weinzierl & Webb (1972).

1.3 Stability

The inorganic nickel salts considered are in general stable except for the efflorescence which may occur with the hydrated materials.

Nickel carbonyl decomposes at temperatures above 60°C. This may occur with explosive force when it is heated rapidly. This material has in fact been reported to be stable only in the presence of carbon monoxide (Brief et al., 1971).

Both nickel carbonyl and nickelocene decompose rapidly in the presence of air, while the latter also decomposes readily in solution.

2. Use and Occurrence

(a) Use

Nickel powder: Nickel powder is produced commercially by the Mond process and its variations. Nickel or nickel ore is reacted with carbon monoxide to nickel carbonyl gas which is then decomposed by heat to obtain pure, finely-divided nickel.

In another method of production, the nickel and cobalt contents of nickel oxide ores are recovered as carbonates, which are calcined to

nickel oxide and reduced to nickel powder.

US imports totalled 6.1 million pounds in 1970.

It is believed that by far the greatest percentage of nickel powder is consumed in the production of other forms of nickel. It is expected that increased shipments and consumption of the powder for production of these forms of nickel will occur in the future.

A principal use of nickel is as an alloying additive in steel manufacture. It is also used in the production of coins, domestic utensils, monel metals and other alloys. Many of these products are manufactured from finely divided nickel powder. Use is also made of nickel compounds in the manufacture of storage batteries, electronic equipment and sparking plugs.

Nickel acetate: Nickel acetate is produced commercially by reacting sodium acetate with a nickel sulphate solution (prepared from nickel sulphate or by dissolving nickel oxide in sulphuric acid). US consumption of all organic nickel salts in 1968 has been estimated at 0.5 million pounds, almost all of which was nickel acetate.

Nickel acetate finds its principal use as a mordant in the textile industry and has a minor use as a hydrogenation catalyst. None of its miscellaneous applications are believed to account for a significant percentage of the total consumed.

Nickel carbonate: Only basic nickel carbonate ($2NiCO_3.3Ni(OH)_2.4H_2O$) is a commercial product. It is largely produced and consumed in the course of manufacturing nickel oxide, nickel powder or nickel catalysts.

Canada is believed to be the largest single producer of this material. It has been estimated that 2 million pounds of nickel were consumed in the US in 1970 in the form of nickel salts other than nickel sulphate. Nickel carbonate is probably the largest single compound included in these nickel salts.

Raney nickel is widely used as a catalyst, and an estimated 2 million pounds of the basic nickel carbonate is used for the production of nickel catalysts for use in organic chemical manufacture, petroleum refining and

edible oil hardening in the US each year.

A high purity basic nickel carbonate is produced for use in electronic components such as ferrites and thermistors. The total nickel carbonate thus consumed is minor, although the number of individuals exposed could be quite high because of the large number of electronic component companies making and using ferrites and thermistors.

Nickel carbonyl: Nickel carbonyl is produced commercially by the Mond process and its variations, as described earlier under nickel powder. Total US production is estimated at less than 15 million pounds.

On a worldwide basis, the significant uses of nickel carbonyl are in the refining of nickel, the manufacture of high purity nickel powder for powder metallurgy fabrication of nickel and nickel alloy components and shapes, and the manufacture of catalysts. In these uses the carbonyl is contained within process equipment with no human exposure for equipment failures. However, the convenience of making the carbonyl and converting it into nickel has resulted in a large number of small-scale uses for the carbonyl, where exposure to personnel and venting to the atmosphere may constitute a hazard (e.g., vapour plating of nickel and depositing of nickel in semiconductor manufacture.

Nickelocene: Nickelocene is currently available only from laboratory-scale synthesis. A commercial production process has been developed, but only sample quantities have been produced. The compound has been advocated as an anti-knock additive for gasoline, but no nickel has been reported in the 300 gasoline additives now registered with the US Environmental Protection Agency.

Nickel oxide: Nickel oxide is generally obtained by roasting refined nickel ores. Partially reduced nickel oxide products known as "nickel oxide sinters" are produced commercially on a large scale. One of the two types contains 75% nickel and the other contains 90% nickel. Available data on nickel oxide products frequently combine information on nickel oxide powder and nickel oxide sinters.

Canada (with one producer) is believed to be the largest single producing country. Total US production (all refined oxide) is estimated

to have been less than 1 million pounds in 1970.

US consumption of imported products in 1970 and 1971 is estimated to have been 16.7 and 15.0 million pounds for nickel oxide and 69.6 and 69.0 million pounds for nickel oxide sinters.

It is believed that most of the nickel oxide sinters goes into the production of stainless and alloy steels.

The US consumption pattern for nickel oxide (excluding sinters) in 1970 is estimated to have been 12, 2.1 and 2.6 million pounds for nickel sulphate, catalysts, enamel frits plus electronic devices, respectively.

Nickel subsulphide: Nickel subsulphide is apparently not made commercially.

Nickel sulphate: Nickel sulphate is produced on a commercial basis by dissolving nickel oxide in sulphuric acid and concentrating the solution to precipitate nickel sulphate heptahydrate, which on heating forms the commercial crystalline nickel sulphate hexahydrate.

In 1970, US production of nickel sulphate was 41.8 million pounds and consumption was estimated at 42.1 million pounds; but US production in 1971 has been reported as only 33.5 million pounds.

The 1970 consumption pattern for nickel sulphate (expressed in millions of pounds) is estimated to have been as follows: plating baths, 35.8-37.8; nickel carbonate catalysts, 3.6; organic nickel salts, 0.5; others, 0.2-2.2; total, 40.1-44.1 million pounds.

Nickel sulphate is not only consumed as such in plating baths but is also used as an intermediate in the production of nickel ammonium sulphate, $NiSO_4.(NH_4)_2SO_4.6H_2O$, and nickel carbonate, which are also used in nickel plating. It is used as an intermediate for depositing nickel carbonate on catalyst substrates and as the principal intermediate for the manufacture of organic nickel salts.

(b) Analytical methods

Trace analysis of nickel may be performed by a number of instrumental techniques of which atomic absorption spectrometry finds increasing

application. The use of atomic absorption spectrometry in the determination of nickel in biological materials is discussed by Sunderman (1965). Colorimetry is less sensitive but less costly, and this is also employed.

Sunderman et al. (1968) described a gas chromatographic method for the detection of nickel carbonyl in blood and breath.

A spectrophotometric method for the measurement of nickel carbonyl in air depends upon the oxidation of the carbonyl to ionic nickel and carbon monoxide (Kincaid et al., 1953). Brief et al. (1971) described a modification of this method.

(c) Occurrence

Nickel

Natural environment: Over 90% of the world's nickel is obtained from pentlandite (FeNi)S, a mineral invariably associated with large amounts of pyrrhotites and varying amounts of chalcopyrite. Nickel is a natural impurity of some types of asbestos, in particular chrysotile (Cralley et al., 1967); and according to Gross et al. (1967) the nickel content of asbestos may be increased further as a result of contamination during milling.

Air: Nickel powder's increasing usage enhances the probability of its appearance in the atmosphere at nickel production plants. The average concentration of nickel in air samples collected from widely scattered location in the US in 1964 and 1965 was 340 ng/m^3 (Falk, 1970). Nickel constitutes 0.03% of the particulate matter suspended in the atmosphere (Sullivan, 1969). Nickel finds its way into the atmosphere as a result of the combustion of coal, diesel oil and fuel oil (Bowen, 1966). In addition, there is evidence that pure nickel powders and iron-nickel powders of less than 1 micron in size are deposited as meteoritic dust from the stratosphere.

Tobacco smoke: Traces of nickel are present in tobacco smoke (Szadkowski et al., 1969). According to Sunderman & Sunderman (1961), six brands of American cigarettes contain on average between 1.59 and 3.07 µg Ni per cigarette, and 20% of this finds its way into the

mainstream smoke. In a burning cigarette all of the reaction conditions which are known to lead to the formation of nickel carbonyl are present.

Water: The concentration of nickel in various samples of water ranged from 0-12.5 µg/kg (Schroeder et al., 1961).

Food: Schroeder et al. (1961) listed nickel levels in various foods and recorded concentrations of up to 6.45 mg/kg in cereal foodstuffs, up to 2.6 mg/kg in vegetables and fish and 5 mg/kg wet weight in cocoa.

Animal tissues: In animal tissues, nickel levels were mostly within the range of 0-3 µg/g wet weight (Schroeder et al., 1961).

Nickel acetate: Nickel acetate does not occur in nature as such.

Nickel carbonate: Nickel carbonate occurs in nature in the mineral zaratite, $NiCO_3.2Ni(OH)_2.4H_2O$. Nickel carbonate is formed by the decomposition of nickel carbonyl in moist air. Thus, the nickel carbonate formed from the carbonyl is a potential atmospheric and surface water pollutant.

Nickel carbonyl: In addition to its appearance as a synthetic intermediate in plants producing nickel and nickel products, nickel carbonyl may be present wherever carbon monoxide contacts nickel and nickel alloys. It is generated and released into the atmosphere as a product of fossil fuel combustion. Such global atmospheric release has been estimated by one source at 140 million pounds per year (calculated as nickel). Since the carbonyl readily decomposes and forms nickel oxide in dry air and/or nickel carbonate in moist air, these latter compounds present the more likely pollutant.

Nickelocene: Nickelocene does not occur in nature as such.

Nickel oxide: The principal natural form of nickel oxide is in admixture with nickel sulphides in varying proportions in weathered ore. Nickel oxide is formed by the decomposition of nickel carbonyl in the atmosphere (see nickel carbonyl).

Nickel subsulphide: Nickel subsulphide is found in nature as the mineral heazlewoodite. It is not a major nickel-bearing mineral, and is

not believed to be a significant atmosphere or water pollutant.

Nickel sulphate: Nickel sulphate is not a naturally-occurring form of nickel. Because of its widespread use in plating baths it may appear as a water pollutant in industrial areas where such baths are discarded or parts are washed after the plating operation.

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Man

3.1 Carcinogenicity and related studies in animals

(a) Inhalation and/or intratracheal administration

Mouse: Hueper (1958) saw no abnormalities of the bronchial mucosa in 20 female C57BL mice exposed to an atmosphere containing 15 mg/m^3 of >99% pure powdered nickel, the majority of particles having a diameter of 4 μ or less, for six hours daily, four to five days per week for up to 21 months. However only three of the mice lived for longer than 12 months. Two cases of lymphosarcomas were regarded as being of "spontaneous" origin. There was no untreated control group.

Rat: Hueper (1958) exposed 50 male and 50 female Wistar rats and 60 female Bethesda Black rats to an atmosphere containing 15 mg/m^3 of >99% pure powdered nickel, the majority of the particles having a diameter of 4 μ or less, for six hours daily, four to five days per week for up to 21 months. Most of the animals (128/160) died before 15 months. The lungs of 15/50 rats of both strains studied histologically developed what the author refers to as "abnormal multicentric adenomatoid formation affecting the alveolar structures and atypical proliferations of the epithelial lining of the terminal bronchioli". In some rats, but not all, "subchronic inflammatory reactions" were associated with the adenomatoid formations. Inflammatory changes and mucosal ulcers were found in the paranasal sinuses. Hueper (1958) regarded the adenomatoid lung lesions as benign neoplasms. There was no excess of neoplasms in other organs. No comparable unexposed groups of rats were included

in the experimental design. The Working Group considered that these lung lesions were not necessarily of a neoplastic nature.

Hueper & Payne (1962) failed to produce lung tumours in 120 rats, 46 of which survived for more than 18 months after exposure for five to six hours per day to 99% pure nickel powder (level unspecified) together with 20-35 ppm of the lung irritant, sulphur dioxide, and with powdered limestone, the latter being added to prevent the nickel particles from forming conglomerates.

Sunderman et al. (1957, 1959) exposed two groups of 64 and 32 male Wistar rats for 30 minutes thrice weekly for one year to nickel carbonyl at concentrations of 0.03 or 0.06 mg/l respectively. A further group of 80 rats was exposed once only to an atmosphere containing 0.25 mg nickel carbonyl/l, this level approximating to the LD_{50}. Animals were observed for up to 30 months after the first exposure. Extensive squamous metaplasia of bronchial epithelium and inflammation were seen in all rats, and four of nine rats that survived for two years developed neoplasms of the lung. One rat had a mixed adenocarcinoma and squamous carcinoma which had metastasized to one kidney and to the mediastinum. A second rat had a similar but more anaplastic tumour. A third rat developed a squamous cell carcinoma, and a fourth two papillary bronchial adenomas. Of 41 control animals only three survived two years, and none showed pulmonary tumours.

Sunderman & Donnelly (1965) observed one pulmonary adenocarcinoma with metastases among 42 male Wistar rats that survived at least two years after a single 30-minute exposure to 80 ppm nickel carbonyl. Of 285 rats exposed, only 71 survived three weeks after exposure. No pulmonary neoplasms were seen in 19 control rats. In another group of 64 male Wistar rats exposed to 4 ppm (0.03 mg/l) nickel carbonyl for 30 minutes three times weekly until death, survival rates at three weeks, one year and two years after the first exposure were 0, 25 and 88% respectively; one pulmonary adenocarcinoma with metastases was seen in a rat which died at 26 months. No

pulmonary tumours were seen in 32 controls of which 22 survived two years. Test and control animals in both experiments showed tumours at sites remote from the lungs. The authors considered that the two pulmonary tumours were due to exposure to nickel carbonyl. The Working Group, however, was unable to accept these findings as acceptable evidence of pulmonary tumour development.

Hamster: Hueper & Payne (1962) saw no lung tumours in 100 hamsters, 66 of which survived for more than 18 months after simultaneous exposure to 99% pure nickel dust (level unspecified), 20-35 ppm sulphur dioxide (acting as a lung irritant) and powdered limestone (to prevent nickel particles from forming conglomerates).

Guinea-pig: Hueper (1958) exposed 32 male and 10 female guinea-pigs of inbred strain 13 to an atmosphere containing 15 mg/m^3 of >99% pure finely powdered nickel of particle size 4 μ or less for six hours per day, four to five days per week for up to 21 months. Only 23 animals survived for more than one year and only two for more than 18 months. At death, practically all the animals were found to have "abnormal multicentric adenomatoid formations affecting the alveolar structures" and hyperplastic changes in the terminal bronchiolar epithelium. One animal had an anaplastic intra-alveolar carcinoma; and another, with extensive pulmonary adenomatosis, showed a nodule in the abdominal cavity that was thought to be a metastasis from a pulmonary neoplasm, although no primary tumour was seen in the lung. There were no controls.

(b) Subcutaneous and/or intramuscular administration

Mouse: Gilman & Ruckerbauer (1962) injected into each thigh muscle of 40 Swiss mice 10 mg of a metallic dust from a flue at a nickel refinery. The dust contained 20% nickel sulphate, 57% nickel subsulphide and 6.3% nickel oxide. There were 36 survivors at 90 days. In all, 23 sarcomas, mainly originating in striated muscle, arose at approximately one-third of the injection sites after an average latent interval of 11 months. Gilman (1962) reported that similar tumours could be induced with either nickel

subsulphide or with nickel oxide alone, the former being the more potent. Treatment consisted of introducing 5 mg of the agent into one or both thigh muscles of Swiss or C3H strain mice. Sarcomas arose at between 23 and 53% of injection sites with both agents. No controls were employed in either experiment.

Rat: Gilman & Ruckerbauer (1962) injected i.m. into each thigh of 66 hooded and 20 Wistar rats 20 or 30 mg of a metallic dust from a flue at a nickel refinery. The dust contained 20% nickel sulphate, 57% nickel subsulphide and 6.3% nickel oxide. Sarcomas, most of them originating in striated muscle, arose at the injection site after an average of only five to six months at approximately half of the injection sites in both rat strains: 52 sarcomas in hooded rats and eight sarcomas in Wistar rats. There were no controls.

Gilman (1962) obtained a similar result by injecting i.m. into one or both thighs 20 mg of either nickel subsulphide or nickel oxide, with latent periods of tumour induction of 150 and 302 days respectively. But no tumours were produced by 5 mg nickel sulphate injected into both thighs of 32 Wistar rats observed for up to 603 days. There were no controls.

Heath & Daniel (1964) injected 28.3 mg of pure powdered nickel suspended in 0.4 ml fowl serum into the right thigh muscles of ten female rats of a hooded strain. All the animals developed tumours at the injection site between 17 and 41 weeks after treatment. All the tumours were derived from striated muscle and most were well-differentiated. Metastasis to prevertebral lymph nodes was seen in three rats. Previous findings in control rats had shown that tumours were not produced after injections of fowl serum alone.

Daniel (1966) compared the response of three different strains of rats to the i.m. injection of 10 mg nickel subsulphide in 0.1 ml aqueous penicillin G procaine into each gastrocnemius muscle. Injection-site tumours developed invariably in both legs of all 28 hooded rats and in one leg only of 14/27 Bethesda Black rats. There were no controls. Moreover, more of the tumours in the hooded

strain were well-differentiated rhabdomyosarcomas. In another experiment, the early response (two to ten weeks) of Fischer rats was found to be more like that of the hooded strain than that of the Bethesda Black strain. Necrosis and abnormal myoblasts were features of the response of Fischer and hooded rats, and active phagocytosis of nickel subsulphide a feature of the response of Bethesda Black rats.

Furst & Schlauder (1971) gave repeated i.m. injections of nickel powder or nickelocene at monthly intervals to 25 male and 25 female Fischer-344 rats. In the case of nickel itself, treatment consisted of five injections each of 5 mg in 0.2 ml trioctanoin, and 38/50 rats developed fibrosarcomata within 11 months of the start of treatment. In the same period 18/50 rats given 12 injections of 12 mg nickelocene in 0.2 ml trioctanoin and 21/50 rats given 12 injections of 25 mg nickelocene in 0.2 ml trioctanoin developed fibrosarcomata. Some of the tumours were successfully transplanted. No fibrosarcomata developed in 50 control rats given 12 injections of trioctanoin.

Hamster: Furst & Schlauder (1971) injected i.m. nickel powder or nickelocene at monthly intervals into groups of 25 male and 25 female hamsters. In the case of nickel, treatment consisted of five injections each of 5 mg in 0.2 ml trioctanoin, and by 11 months after the first injection two males developed fibrosarcomata. Of 50 controls given nine i.m. injections of 0.2 ml trioctanoin, none developed tumours. Of 50 hamsters given a single injection of 25 mg nickelocene in 0.2 ml trioctanoin, 29 survived for 11 months and of these four developed fibrosarcomata. Of 50 hamsters given eight injections of 5 mg nickelocene in 0.2 ml trioctanoin, none developed local tumours.

(c) Other experimental systems

Intravenous injection: Hueper (1955) saw no neoplasms in response to two intravenous injections of 0.05 ml of a 0.005% nickel powder in 2.5% gelatin in 25 C57BL male mice, 19 of which lived for more than one year and six of which lived for more than 15 months.

There were no controls.

Hueper (1955) injected 0.5 ml/kg bw of a 0.5% nickel suspension in physiological saline into 25 Wistar rats at weekly intervals for six weeks. The only neoplasms that could be attributed to treatment arose seven to eight months after the first injection in seven rats near the site of injection (region of groin) where seepage of the injected material had occurred. Deposits of black powder in the lungs indicated that at least some of the injected material stayed in the vein at the time of injection. There were no controls.

Lau et al. (1972) injected six doses of 20 µl/kg bw (9 mg nickel/kg bw) of nickel carbonyl into 61 male and 60 female Sprague-Dawley rats which were observed until death. In all, 19/21 (16%) rats surviving the six injections developed malignant tumours. The tumours included six undifferentiated sarcomas of various sites, three fibrosarcomas of various sites, one liver carcinoma, one kidney carcinoma, one mammary carcinoma, one haemangioendothelioma and five pulmonary lymphomas. Among 47 sham-injected control rats the only malignant tumours were two lung lymphomas. The difference in incidence in malignant tumours between treated and control rats was regarded by these workers as being statistically significant ($P=0.02$); but the Working Group questioned the validity of this comparison because the treated animals constituted a selected group.

Hueper (1955) saw no neoplasms in ten rabbits given weekly injections of a 1% nickel suspension (0.5 ml/kg bw) in 25% aqueous gelatin solutions for six weeks. Only four of the rabbits survived for more than two years. No effects were seen in five control rabbits in up to 40 months.

Intrapulmonary administration: Hueper & Payne (1962) introduced finely powdered nickel directly into the lungs of 34 Bethesda Black rats by thoractomy. Survivors were similarly treated one year later. Of 14 rats that lived for 18 months or more after the first injection, one developed a sarcoma at the site of injection. No epithelial tumours of the lung were seen. There were no controls.

Intrapleural administration: Hueper (1955) saw no neoplasms attributable to treatment in 50 C57BL male mice, 33 of which survived for more than one year and four of which survived for more than 18 months, after a single injection of 0.02 ml of a 0.06% suspension of nickel powder in 2.5% gelatin-saline solution.

Hueper (1952) reported tumour formation in 4/12 female Osborne-Mendel rats that died between seven and 16 months after five monthly injections of 0.05 ml of a 12.5% (by volume) suspension of powdered nickel in lanolin. The tumours were round or spindle-cell sarcomas.

Intramedullary injection into the femur: Hueper (1952) reported osteosarcomas in 3/17 rats surviving seven months following an injection of 0.05 ml of a 12.5% (by volume) suspension of powdered nickel in lanolin. This finding was not confirmed in a subsequent study by Hueper (1955) who reported that 27/100 rats, 40 of which survived for more than 18 months, developed neoplasms at or near the site of injection of 0.1 ml of a 5% suspension of nickel powder in 20% gelatin-saline. The author commented that there was usually some seepage of suspension from the marrow cavity into the periosteal tissue. Sixteen of the tumours were fibrosarcomas, four were rhabdomyosarcomas, five were thought to be neurogenic in origin, one was an angiosarcoma and one was a recticulum-cell sarcoma. Metastases were seen in 14/27 rats bearing injection-site tumours. In addition, 20 neoplasms seen at sites remote from the injection site were not considered to be causally related to nickel.

Hueper (1955) reported that 1/6 rabbits given two injections, 27 months apart, of 0.25 ml powdered nickel in lanolin (12.5% nickel, by volume) developed a metastasizing endosteal fibrosarcoma of the femur. Two rabbits given injections of lanolin alone failed to develop a local tumour.

Implantation: Gilman (1966) reported the occurrence of rhabdomyosarcomas in 2/45 and fibrosarcomas in 14/45 Swiss mice given a single i.m. implant of 5 mg nickel subsulphide, and five

rhabdomyosarcomas and 16 fibrosarcomas among 50 Swiss mice similarly treated with nickel oxide. There were no controls.

Gilman & Herchen (1963) induced tumours in rats by the implantation into both gluteal regions of nickel subsulphide administered either as a 10 mg powder with particles of 2-4 μ diameter, 500 mg as 3-5 mm diameter fragments, 500 mg as single discs or as a 10 mg powder within a millipore diffusion chamber. Rhabdomyosarcomas arose in approximately 70% of implantation sites in all four groups. Several tumours gave rise to distant metastases. Only 1/20 control rats that received implants (two per rat) consisting of empty diffusion chambers developed a tumour.

Herchen & Gilman (1964) implanted solid discs of compressed nickel subsulphide powder (measuring 8 x 1 mm and weighing approximately 250 mg) into the right gluteal regions of 120 inbred Fischer rats. The implants were removed from groups of ten rats after 2, 4, 8, 16, 32, 64, 128 and 256 days. Palpable local tumours arose in four, seven and ten rats respectively of the last three groups. For control purposes similarly sized discs of ferric oxide were implanted into the left gluteal regions of the same animals. No local tumours arose at the sites of ferric oxide implants, irrespective of how long they remained in situ.

Gilman (1966) referred to the induction of rhabdomyosarcomas in 9/17 and fibrosarcomas in 3/17 rats following the introduction (presumably into the thigh muscles) of millipore diffusion chambers containing nickel subsulphide. This observation was taken to indicate that direct contact between metal particles and cells is not necessary for carcinogenesis. The same paper reports the induction of tumours, mostly rhabdomyosarcomas, in 19/30 Wistar rats given subsulphide and rhabdomyosarcomas in 14/32 and fibrosarcomas in 4/32 Wistar rats given nickel oxide. A dose-response relationship was found with nickel subsulphide-induced rhabdomyosarcomas: 10 mg per site gave an 80% tumour incidence. Nickel-induced rhabdomyosarcomas metastasize freely, especially to the lungs. There were no controls.

3.2 Other relevant biological data

(a) Animals

After a single i.v. dose of 0.74 or 1.47 µg of ^{63}Ni as nickel chloride to rats, 61% of the dose was excreted in the urine and 5.9% in the faeces within 72 hours (Smith & Hackley, 1968). Radioactivity disappeared from the blood completely within 48 hours. Of the major organs, only the kidneys contained significant amounts of ^{63}Ni after 72 hours. The adrenals retained more nickel than might have been expected, but the tissue level of nickel declined at a rate comparable with that for other tissues.

Nickel powder (5 mg) and molar equivalents of nickel acetate and nickelocene were injected i.m. into rats (Chen et al., 1971). After 24 to 36 hours, daily excretion of nickelous ion in rat urine was 30, 150 and 400 µg/day respectively. After about ten days, the rat effectively stopped excreting both nickel compounds. The urinary nickel concentration from the nickel powder injected rat remained constant for over a month.

Sunderman & Selin (1968) studied the tissue distribution and excretion of ^{63}Ni in rats exposed to a LD_{50} dose of $^{63}Ni(CO)_4$ by inhalation or by i.v. injection. About 38% of an i.v. dose of $^{63}Ni(CO)_4$ was exhaled in the expired air within six hours of dosage. Within four days of dosage, 31% of the dose was excreted in the urine and 2% in the faeces. At one hour after inhalation of $^{63}Ni(CO)_4$, 48% of blood ^{63}Ni was present in the erythrocytes, compared with only 8% in the erythrocytes at six hours. At six hours, ^{63}Ni in blood serum was predominantly bound to albumin. At 24 hours, ^{63}Ni in lung and liver homogenates was partially bound to RNA, DNA, and protein.

Kasprzak & Sunderman (1969) reported that after an i.v. LD_{50} dose of $Ni(^{14}CO)_4$ to rats approximately two-thirds of the dose is split into nickel and carbon monoxide and the latter combines with haemoglobin to form carboxyhaemoglobin, the concentration of the latter being maximal two hours after injection. Within six hours after injection, 49% of the administered dose was exhaled as ^{14}CO

and only 1.1% as $^{14}CO_2$. At 24 hours after dosage <1% of the dose was excreted in the urine.

Following two daily seven-hour inhalation exposures of nickel oxide dust totalling 61.74 mg-minute/l to hamster, >70% of the dose was present in the lungs at six days post-exposure (Wehner & Craig, 1972).

After acute or chronic exposure of rats to nickel carbonyl by inhalation, increases in nickel occur predominantly in the microsomal and supernatant fractions of lung and liver. After chronic exposure increased amounts of nickel are also observed in nuclear and mitochondrial fractions of the lung (Sunderman & Sunderman, 1963). RNA derived from the lungs of rats exposed to nickel carbonyl showed abnormal physico-chemical properties (Sunderman, 1963).

Nickel carbonyl inhibits the synthesis of hepatic RNA, as demonstrated by the inhibition of cortisone induction of hepatic tryptophan pyrrolase (Sunderman, 1967a), inhibition of [^{14}C]orotic acid incorporation in vivo into liver RNA (Beach & Sunderman, 1969) and inhibition of DNA-dependent RNA-polymerase activity in hepatic nuclei (Sunderman, 1971). Beach & Sunderman (1970) have shown that the inhibition of RNA synthesis persists after the disruption of hepatic nuclei, and they exclude the possibility that inhibition is due to impaired transport of RNA precursors across the nuclear membrane. Nickel carbonyl resembles actinomycin D in its differential effects upon hepatic synthesis of RNA (high inhibition) and proteins (low inhibition) and in its similar inhibitory effects on liver enzyme induction (Sunderman, 1971).

Hackett & Sunderman (1968) reported that i.v. administration to rats of nickel carbonyl in LD_{50}-LD_{100} doses led to diffuse dilatation of the rough endoplasmic reticulum and nucleolar shrinkage in hepatic cells. Sunderman (1967b) found that inhalation of nickel carbonyl inhibited the phenothiazine induction of benzpyrene hydroxylase in the lungs and livers of rats.

Sunderman et al. (1961) reported that after inhalation exposure to nickel carbonyl pathological changes are most marked in the lungs; the adrenal glands and kidneys are affected to a lesser degree. Changes in the alveolar epithelial cells are striking.

The total level of nickel in the urine was found to be increased. An i.v. LD_{50} dose of nickel carbonyl (22 mg nickel/kg bw) led to intense swelling and to proliferation of alveolar endothelial cells (Hackett & Sunderman, 1968).

Kincaid et al. (1953) reported the inhalation LD_{50}s of nickel carbonyl for a 30-minute exposure to be 0.067, 0.24 and 1.9 mg/l in mice, rats and cats, respectively.

For a few lower organisms nickel appears to be essential for growth (Bartha & Ordal, 1965; Kotala & Luba, 1965). The work of others (e.g., Schwartz & Bodansky, 1964; Yoneda, 1964), however, suggests that nickel either has no effect on growth of higher organisms or inhibits it.

(b) Man

Increased concentrations of nickel in serum after myocardial infarction (Sunderman et al., 1970) and in cases of stroke, burns, hepatic cirrhosis and uraemia (McNeely et al., 1971) suggest that nickel is released when normal tissues are damaged. In 15 workers exposed occupationally for several months to nickel carbonyl, urinary levels of nickel ranged from 4 to 224 µg/100 ml; but normal levels were restored after withdrawal from exposure (Ghiringhelli & Dakli, 1956).

3.3 Observations in man

Ten cases of nasal cancer among workers in a large nickel refining company in South Wales were described in the Report of the Chief Inspector of Factories and Workshops for 1932 (Chief Inspector of Factories, 1933). By 1950, a total of 52 cases of nasal cancer and 93 cases of lung cancer had been reported from the refinery (Chief Inspector of Factories, 1952); these were considered to be industrial diseases by

the Minister of Pensions and National Insurance. Morgan (1958) and Doll (1958) found that the relative frequency of deaths from lung cancer or nasal cancer was significantly higher than in the male population at large. Doll et al. (1970) undertook a follow-up study of 845 men employed at the refinery for at least five years and who were first employed before 1944. They observed that in men employed before 1925, deaths from lung cancer were about five to ten times the numbers expected from national rates, while deaths from nasal cancer were 100 to 900 times the expected figures. Men employed in 1925 or later showed no excess in mortality from these cancers. The results confirmed previous suggestions (Morgan, 1958; Doll, 1958) that the cancer hazard in the refinery had been effectively removed by 1925. Furthermore, among workers exposed before 1925, the risk of developing nasal cancer persisted more or less unchanged for 15 to 42 years after the carcinogen was eliminated, whereas the risk of developing lung cancer decreased over time, possibly due to the differential elimination of heavy cigarette smokers by deaths from smoking-related disease (Doll et al., 1970).

The lung cancers related to occupational nickel exposure have been usually squamous cell carcinomas (Williams, 1958); the "nasal" cancers have been undifferentiated or squamous cell carcinomas of the nasal sinuses, especially the ethmoid sinus (Sunderman, 1968).

Although the exact nature of the carcinogenic agent in nickel refineries is unknown, the cancer hazard has been associated with the earliest stage of refining which involves heavy exposure to dust from relatively crude ore (Doll et al., 1970). The view that nickel carbonyl is alone responsible has been discounted due to the disappearance of cancer risk despite continued use of the carbonyl process after 1925 in South Wales and due to the detection of an excess risk of respiratory cancer in refineries using the electrolytic and not the carbonyl process in Canada (Mastromatteo, 1967) and other countries (reviewed by Sunderman, 1968; Doll et al., 1970). In some nickel refineries, the high levels of arsenic or other agents may influence the cancer risk (Morgan, 1958; Rockstroh, 1958), but most investigators have favoured the view that nickel in some form is primarily responsible.

4. Comments on Data Reported and Evaluation

4.1 Animal data

Evidence of tumour induction in the lungs of mice, rats, hamsters or guinea-pigs following inhalation of powdered nickel alone or in combination with sulphur dioxide and powdered limestone is regarded as inconclusive. Two inhalation studies in rats on nickel carbonyl failed to produce conclusive evidence of pulmonary tumour development.

No information on long-term feeding studies was available to the Working Group.

Injection i.m. of nickel powder, nickel subsulphide, nickel oxide or nickelocene into mice or rats may result in the appearance of fibrosarcomas and/or rhabdomyosarcomas. The fact that a variety of nickel compounds produce local tumours suggests that nickel in some form is the active agent. This is also supported by the fact that sarcomas arose around millipore diffusion chambers containing nickel subsulphide. The results of the studies in which nickel powder or nickelocene was injected i.m. into hamsters are regarded as inconclusive.

The observation that repeated i.v. injections of nickel carbonyl induces tumours in rats was also regarded as inconclusive by the Working Group.

No conclusive evidence of tumour formation was found when nickel powder was introduced into the femoral or pleural cavity of rats.

4.2 Human data

In the past, there has been an excessive risk of cancers of the nasal sinus and lung among nickel refinery workers who inhale nickel-containing dusts from crude ores. It is probable that nickel in some form is carcinogenic.

There is no evidence to suggest that non-occupational exposure to nickel constitutes a cancer hazard.

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TETRAETHYL- AND TETRAMETHYLLEAD[*1]

1. Chemical and Physical Data

Tetraethyllead (TEL)

1.1 Synonyms

Chem. Abstr. No.: 78-00-2

Lead tetraethyl, TEL, plumbane tetraethyl

1.2 Chemical formula and molecular weight

$Pb(C_2H_5)_4$ Mol. wt: 323.45

1.3 Chemical and physical properties of the pure substance

(a) Description: A colourless oily liquid with a pleasant odour which burns with an orange-coloured flame with a green margin.

(b) Melting-point: $-130^{\circ}C$

(c) Boiling-point: About $200^{\circ}C$

(d) Flash-point: $77^{\circ}C$

(e) Density: ($20^{\circ}C$) : 1.653

(f) Solubility: Insoluble in water; soluble in most organic solvents.

(g) Refraction: n_D^{20} : 1.5198

(h) Stability: Decomposes slowly at room temperature and more rapidly at elevated temperatures. Combustible.

Tetramethyllead (TML)

1.1 Synonyms

Chem. Abstr. No.: 75-74-1

Lead tetramethyl, TML, plumbane tetramethyl

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[*] Considered by the Working Group in Lyon, December 1972.

[1] An evaluation of inorganic lead compounds appeared in Volume 1 of the IARC Monographs on The Evaluation of Carcinogenic Risk of Chemicals to Man.

1.2 Chemical formula and molecular weight

$Pb(CH_3)_4$ Mol. wt: 267.37

1.3 Chemical and physical properties of the pure substance

(a) Description: Colourless liquid

(b) Melting-point: $-27.5^{\circ}C$

(c) Boiling-point: $110^{\circ}C$ (10 mm)

(d) Flash-point: $38^{\circ}C$

(e) Density: 1.99

(f) Solubility: Insoluble in water; slightly soluble in benzene, petroleum ether and ethanol; soluble in gasoline.

(g) Stability: Somewhat more stable than the tetraethyl compound. Combustible.

2. Use and Occurrence

(a) Use

TEL: TEL is produced commercially either by treating ethyl chloride with a lead-sodium alloy or by electrolysis of an ether solution of a Grignard reagent (ethyl magnesium chloride) using a lead anode.

US production of TEL in 1971 was estimated to be 520 million pounds. Data on the production of TEL in the rest of the world are unavailable, although such production probably does not exceed 200 million pounds per year.

Either directly or indirectly, virtually 100% of the TEL produced in the US is used to make anti-knock additives for gasolines. Some TEL is mixed directly with lead scavengers (usually ethylene dichloride and ethylene dibromide) to make one type of additive containing about 65% TEL. Another type of additive is made by mixing TEL with TML to produce physical mixtures containing 10-75% TML. The additives made from these mixtures contain 40-50% of lead scavengers.

The rest of the TEL is used to make so-called "redistribution reaction mixtures" by reacting the TEL with varying amounts of TML. The resulting

mixed lead alkyls include some unchanged TEL and TML and some compounds that have methyl and ethyl groups in the same molecule (i.e., trimethylethyllead, dimethyldiethyllead and triethylmethyllead). These reaction mixtures are also compounded with lead scavengers to make yet another type of anti-knock additive. Most commercial US gasolines contain anti-knock additives at up to 4 ml/gallon. The additive tends to prevent the pre-ignition of the gasoline in the combustion chamber of the motor. The use of TEL (and TML) is expected to decline rapidly in the US when new air pollution control regulations require gasolines to contain less lead.

Very small amounts of TEL are also used to make other metal alkyls, such as ethylmercury compounds. These compounds are effective fungicides for controlling seed-borne fungi, especially of cereals. However, recently the registrations for mercury-containing fungicides have been cancelled or are under review by US governmental agencies. Consequently, the future use of TEL in the manufacture of these compounds is in jeopardy. However, commercial quantities of the substance are available only in the form of premixed formulations.

TML: TML is produced commercially by the same processes that are used to make TEL except that methyl chloride is substituted for ethyl chloride (see the discussion of TEL for a description of these processes and the by-products obtained).

US production of TML has been increasing steadily since its introduction as a substitute for TEL in 1960 and reached an estimated 200 million pounds in 1971.

Data on production of TML in the rest of the world are unavailable, although such production probably does not exceed 100 million pounds per year.

The usage pattern for TML is identical with that for TEL, except that it is preferentially used in aviation and premium gasolines as a result of its superior performance in gasolines having a high aromatic hydrocarbon content. (See the discussion of TEL for examples of additive formulations and a description of the function of additives in gasolines).

(b) Analytical methods

Cholak (1964) recommended three different methods for the analysis of lead: dithizone method; spectrographic procedures; polarographic method. To this list, atomic absorption spectrometry should now be added (Portmann, 1971).

Kehoe & Thamann (1931) described a selective method for the extraction of TEL using benzene, and Bolanowska et al. (1967) described a method for estimating TEL in biological fluids.

(c) Occurrence

Natural environment: Neither TEL nor TML occurs in nature.

Air: When gasoline containing TEL is burned, all of the TEL is converted to either lead halides or lead phosphates (if organophosphorus compounds have also been added to the gasoline). About a quarter of the added lead is retained within the exhaust systems and engine oil of motor cars (Hirschler & Gilbert, 1964). The remainder is discharged via the exhaust mainly in the form of fine particles of lead compounds. Half of the lead particulate matter falls to the ground within a few hundred feet of the roadway and is washed away and dispersed in the soil and drains. Finer particles are dispersed in the atmosphere and may be carried considerable distances by air movements before they are eventually deposited.

Some unchanged TEL does enter the urban atmosphere as part of the gasoline vapours that escape from gas tanks during filling and as the result of evaporation of spills. The average concentration of gaseous, organic lead in the atmosphere of the Los Angeles basin in 1965 was determined to be 0.077 µg of lead/m^3 of air over a two-month period.

Plants and soil: In plants and soil located 200 m from a factory manufacturing anti-knock compounds, TEL was found at levels of 38 mg/kg and 2 mg/kg respectively, whilst at 800 m, 0 mg/kg in soil and 1 mg/kg in plants were found (Lee, 1972).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Man

3.1 Carcinogenicity and related studies in animals

(a) Subcutaneous and/or intramuscular administration

Newborn mouse: Epstein & Mantel (1968) injected TEL dissolved in tricaprylin subcutaneously into Swiss mice on one to four occasions between birth and 21 days. After a single injection of 2 mg on the first day of life, all of 69 mice died before weaning. Total doses of 1.2 mg given in four divided doses killed 92% of mice before weaning, and doses of 0.6 mg given in four divided doses killed 20% of mice. Of 41 female mice which survived for 36 weeks after treatment with 0.6 mg TEL, five (12%) developed malignant lymphomas at between 36 and 51 weeks. Of 48 female control mice that received injections of tricaprylin alone, none developed lymphomas. Lymphomas developed in 1/39 control males and 1/26 males given a total dose of 0.6 mg TEL. Exposure to 0.6 mg TEL did not increase the risk of hepatomas in males above the control incidence (two hepatomas in 29 control males; one hepatoma in 26 test males); no hepatomas appeared in females of the control or test groups.

The dose in response to which an excessive incidence of tumours occurred was within the lethal range. The type of tumour (i.e., lymphoma) which occurred in increased incidence is, in mice, caused primarily by a virus, and the effect was confined to the female sex. The risk of development of malignant lymphoma in mice is influenced by sex hormone status, by adrenal gland status and by thymic status (see Miller, 1961 for review).

3.2 Other relevant biological data

(a) Animals

After intravenous injection into rats, TEL is converted into triethyllead, which is considered to be responsible for the toxic effects seen (Cremer, 1959). According to Bolanowska (1968), after the intravenous injection of TEL into rats 18% of the administered lead is

converted into an inorganic form. Excretion, principally as triethyllead, occurs via the urine and faeces. After i.v. injections of 25 mg/kg bw of TEL into rabbits the main metabolite was triethyllead, but little of this metabolite was excreted in the urine (Bolanowska & Garczynski, 1967).

Davis et al. (1963) exposed groups of ten rats for seven hours per day for 10-150 days to atmospheric concentrations of 12-63 mg/m^3 of TML; the greater the exposure level the shorter was the duration of exposure. The mean urinary lead excretion ranged from 2 to 8 mg/l in a dose related manner. The same workers exposed six dogs daily for seven hours to 4, 12, 23 or 44 mg/m^3 of TML for up to 100 days, and the average urinary lead concentrations ranged from 0.6 to 4.0 mg/l, being higher for greater exposure levels without a clear dose-response relationship. In similar studies in rats exposed to 12-46 mg/m^3 of TEL for five to 150 days, the average urinary level of the group exposed to 12 mg/m^3 for 15 days was 5.22 mg/l; whilst in dogs exposed to 12-42 mg/m^3 of TEL for up to 30 days, urinary levels of lead ranged from 2.29 to 10.2 mg/l. No correlation was found between exposure level and the urine lead concentration (Davis et al., 1963).

Repeated oral doses of 0.0017-0.17 mg/kg bw of TEL and 0.001-1.08 mg/kg bw of TML to rats five times per week for 20 weeks resulted in the deposition of lead in the liver, kidney, brain, testis and other organs. The distribution of lead in tissues differed between TEL and TML and varied with dose, dose schedule and sex of exposed animals (Schepers, 1964). Magistretti et al. (1963) found that six and 24 hours after intraperitoneal injection of 10 mg/kg bw of TEL and 50 mg/kg bw of TML, the distribution of lead in the tissues was similar for both compounds, being highest in the liver and lowest in the brain. Within 24 hours of i.v. administration of TEL to rats 50% of the total lead in the soft organs was in the form of triethyllead, and 70% of the muscle lead appeared as triethyllead; highest levels were found in the liver, blood, kidney and brain (Bolanowska, 1968). After one week 90-100% of the total lead in the organs was in the form of triethyllead (Bolanowska & Garczynski, 1967).

In rats, following inhalation of 12-63 mg/m^3 of TML for seven hours per day for 10-150 days, the mean lead concentrations of the pooled major tissues ranged from 0.7 to 10.0 mg/100 g tissue in a dose-related manner, i.e., the higher the dose the higher the tissue level. Dogs similarly exposed to 4-44 mg/m^3 of TML for up to 100 days showed pooled tissue lead concentrations of 0.69-1.03 mg/100 g tissue which were unrelated to the dose level. The blood lead concentrations ranged from 0.04 to 0.13 mg/100 g tissue and were also unrelated to the exposure levels. In similar studies with TEL, rats were exposed for seven hours daily to 46, 22 and 12 mg/m^3 for 5, 14 and 150 days respectively. Average lead levels in pooled major tissues ranged from 0.78 to 2.99 mg/100 g tissue. In four dogs exposed for seven hours daily to 42, 22 and 12 mg/m^3 of TEL for 7, 30 or 24 days respectively, pooled major tissue levels of lead ranged from 0.67 to 2.96 mg/100 g tissue and blood levels from 0.06 to 0.14 mg/100 g, but no correlation was found between exposure level and tissue on blood level (Davis et al., 1963).

Rats given dermal applications of 0.1 ml TEL (106 mg lead)/ rat showed highest lead levels in the blood, kidney, liver, lung and brain in that order; about 6.5% of the dose applied was accounted for by the tissues, carcass and treated skin. Thus a substantial proportion of the dose applied appeared to be lost by evaporation from the skin (Laug & Kunze, 1948). When rabbits received a dermal application of 0.75 mg TEL for four hours and were killed from six hours to 205 days later, tissue lead levels reached a peak after 18 hours except in the spleen and bone, where the highest levels were attained after seven and 30 days, respectively (Kehoe & Thamann, 1931).

Magistretti et al. (1963) found in rats that TEL was two to four times more toxic than TML by the i.v. or i.p. route, and that TEL was two to three times more toxic than TML by the oral route. Schepers (1964) found TEL ten times more toxic than TML on oral administration to rats. After single doses within the lethal range of either compound (17 mg/kg bw of TEL; 108 mg/kg bw of TML) rats

showed irritability, hypermobility, tremors and spasticity. After single doses of 1.7 mg/kg bw of TEL or 10.8 mg/kg bw of TML, no behavioural changes were seen. Repeated exposure at these lower levels, however, was associated with behavioural changes, peripheral hyperaemia and excessive body weight gain. No macroscopic changes were seen in most animals killed 21 weeks after the start of exposure. Cardiac hypertrophy, hyperaemia and oedema of the brain, and changes in the liver, pancreas, thyroid, lungs and thymus were seen in a few rats. Microscopically, changes attributable to exposure to TEL or TML were noted in the central nervous system and liver.

(b) Man

deTreville et al. (1962) found that the blood lead concentrations were little affected by the levels of TEL or TML in the expired air. In cases of TEL intoxication in man urinary lead levels are high but blood lead levels may be normal or only slightly raised (Sanders, 1964). In a plant manufacturing TEL a nearly linear relationship was found between the atmospheric level of the TEL and urinary lead excretion in exposed workers (Linch et al., 1970). Blokker (1972) reports that organic lead exposure is reflected better in urinary levels than in blood levels. Lehnert et al. (1970) reported raised blood lead levels and raised urinary excretion of δ-aminolaevulinic acid in urban street sweepers and garbage loaders who, by reason of their occupations, are heavily exposed to vehicle exhaust fumes.

In cases of accidental poisoning with TEL, the liver, kidney, pancreas, brain and heart accumulate triethyllead, and the total tissue lead concentrations correlate with triethyllead concentrations in the corresponding tissues (Stasik et al., 1969; Bolanowska et al., 1967). Studies in cases of TEL poisoning reveal that organically-bound lead does not interfere with iron incorporation into protoporphyrin or with other stages of haem synthesis, as shown by normal urinary levels of δ-aminolaevulinic acid, porphobilinogen and coproporphyrin (Gutniak et al., 1964).

deTreville et al. (1962) found that, in man, TEL is approximately three times more toxic than is TML.

According to Sanders (1964) TEL intoxication in man is characterised by insomnia, excessive dreaming, emotional instability and increased physical activity of an erratic nature. After heavy exposure death may occur in coma, otherwise eventual recovery from the psychotic state is the rule.

(c) Comparative data

Tissue distribution studies of lead in rats and dogs exposed to lethal inhalation doses of TEL or TML and in men fatally poisoned by TEL revealed lead levels of 0.7-13.0 mg/100 g tissue in lung, brain, liver and kidney in the three species. Human lead levels in brain, liver and kidney resembled those seen in corresponding rat and dog tissues (Davis et al., 1963).

3.3 Observations in man

Several cases of acute toxicity, usually in the form of encephalopathy, have been described following occupational exposure to TEL and TML. However, no studies on the occurrence of cancer in exposed individuals have been reported.

4. Comments on Data Reported and Evaluation

4.1 Animal data

The Working Group was not aware of any adequate inhalation study on TEL or TML.

The Working Group could not evaluate the significance of the development of lymphoma in female Swiss mice given TEL s.c. shortly after birth, because this type of tumour occurs spontaneously and in variable incidence in this strain of mouse.

4.2 Human data

Accidental exposure to toxic doses of TEL or TML may occur during their addition to gasoline. No studies to assess the cancer experience of exposed individuals have been reported.

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IRON-CARBOHYDRATE COMPLEXES*

1. Chemical and Physical Data

1.1 Identity

Chemical name	Chem. Abstr. No.	Approx. mol. wt.	Synonyms
Iron-dextran complex	PM 9004-66-4	180,000[1]	Dextran iron complex Iron dextran injection Ironorm injection
Iron-dextrin complex	MX 8050-93-9	230,000[1]	Dextriferron Dextriferron injection Iron carbohydrate complex Iron dextrin injection
Iron-sorbitol-citric acid complex	1338-16-5	<5000[1]	Glucitol iron complex, compound with citric acid Inj. Ferr. Sorbitol Iron sorbitex Iron sorbitol Iron sorbitol citrate
Saccharated iron oxide	MX 8047-67-4	-	Feojectin Ferric oxide, saccharated Ferric saccharate-iron oxide mix. Iron saccharate Iron sugar Proferrin Saccharated iron

Iron-dextran complex

1.2 Chemical composition

A complex of ferric hydroxide with dextrans of average molecular weight 5000-7500 (Martindale, 1972). Dextrans are polysaccharides produced by bacterial action on sucrose. A typical product contains 5% (w/v) iron and 20% (w/v) dextran, molecular weight 6500-7600 (Baker et al., 1961).

*Considered by the Working Group in Lyon, December 1972.

[1]Data from Lundin (1961).

1.3 Chemical and physical properties

(a) Description: The product for human use is a sterile, dark-brown colloidal solution in saline, having a pH of 5.2-6.5 and usually containing 0.5% phenol as a preservative. The products designed for animal use are apparently more concentrated.

(b) Solubility: Extremely soluble in water; insoluble in most organic solvents.

(c) Stability: The complex is unstable at pH 5. It does not undergo autoxidation at ambient temperatures, but this does occur at 65-70° (Jones et al., 1963).

Iron-dextrin complex

1.2 Chemical composition

A complex of ferric hydroxide with dextrins. Dextrins are carbohydrates produced by the partial hydrolysis of starch. It is iso-osmotic with serum and contains the equivalent of 20 mg iron/ml. The pH is about 7.6 (Martindale, 1972).

1.3 Chemical and physical properties

Description: The product for human use is a sterile, clear, dark-brown colloidal solution.

Iron-sorbitol-citric acid complex

1.2 Chemical composition

A complex of ferric iron, sorbitol and citric acid, stabilised with dextrin and sorbitol containing 5% (w/v) of iron.

1.3 Chemical and physical properties

Description: The product for human use is a sterile, brown colloidal solution with a pH of 7.2-7.9 (Martindale, 1972).

Saccharated iron oxide

1.2 Chemical composition

No data available to the Working Group.

1.3 Chemical and physical properties

(a) Description: A reddish-brown powder containing 2.8-3.2% iron.

(b) Solubility: Soluble in hot water, practically insoluble in alcohol.

(c) Stability: Solutions are unstable in the presence of electrolytes.

2. Use and Occurrence

(a) Use

Iron-dextran complex: This substance is a synthetic commercial product which is probably produced by treating a solution of a water-soluble iron salt (e.g., ferric chloride) and dextran with an alkaline material (sodium hydroxide or sodium carbonate) and purifying the resulting complex (e.g., by dialysis).

Iron-dextran complex was introduced in the US in 1957, but it was temporarily withdrawn from the market in 1960 when it was reported to cause sarcomas in rats and mice at the site of repeated s.c. or i.m. injections. The risk of malignancy in man was believed to be very low, and the product was reintroduced in 1962.

Iron-dextran complex is a parenteral form of medication (for i.m. injection only) used in iron-deficiency anaemia in humans and baby pigs. The therapeutic dose is 1-5 ml (50-250 mg iron) daily by deep i.m. injection (Martindale, 1972). Parenteral iron preparations have potential side-effect problems and are recommended for humans only when oral administration is not effective or is contraindicated. Such cases are reported to be very limited.

In April 1972, the US Food and Drug Administration approved an application for the veterinary use of a more concentrated iron-dextran injection in baby pigs. In August 1972, a similar application for use of a related compound, iron hydrogenated dextran injection, in baby pigs was also approved.

Although no data are available on the relative amounts consumed in human or veterinary applications, it has been estimated that the total iron-dextran complex market for the US amounted to 3.2 million dollars in 1967.

Iron-dextrin complex: This substance is a synthetic commercial product. It is no longer known to be offered for sale in the US.

Iron-dextrin is a parenteral form of medication (for i.v. injection) used in iron-deficiency anaemia in humans. The therapeutic dose is 1-5 ml (30-100 mg iron) i.v. daily (Martindale, 1972). Parenteral iron preparations have potential side-effect problems, as mentioned earlier.

No data are available on the quantity of iron-dextrin sold, but it is believed that the product was probably discontinued by the manufacturer because of low sales volume.

Iron-sorbitol-citric acid complex: This substance is a synthetic commercial product which is believed to be produced in Europe.

The complex is a parenteral form of medication (for i.m. injection) used in iron-deficiency anaemia in humans. The therapeutic dose is 1-2 ml daily by deep i.m. injection (Martindale, 1972). Parenteral iron preparations have potential side-effect problems, as mentioned earlier.

Saccharated iron oxide: Although saccharated iron oxide products apparently were produced in the US in the past, no evidence could be found that they are presently being produced or marketed in that country.

Two products containing saccharated iron oxide are believed to have been marketed in Europe in 1969. One of these contained saccharated iron oxide and several other ingredients and was recommended for oral consumption (therapeutic dose 0.6-2.0 g) in the treatment of anaemia. The other product contained 2% saccharated iron oxide in solution and was recommended for parenteral use in the treatment of anaemia. Certain preparations are designed for i.v. administration. The therapeutic dose is 5 ml of a 2% solution containing the equivalent of 100 mg iron daily, usually 20 mg then increasing up to 200 mg iron daily (Martindale, 1972).

Although saccharated iron oxide apparently was used in the US for treatment of anaemia in the past, it reportedly was largely replaced by iron-dextrin. Neither material is now known to be offered for sale in the US.

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Man

3.1 Carcinogenicity and related studies in animals

Subcutaneous and/or intramuscular administration

Mouse:

(a) Iron-dextran complex: Haddow & Horning (1960) found 41 sarcomas, six histiocytomas and one epithelioma at the injection site in 70 out of 95 mice that survived from six to 18 months after the start of a course of once-weekly s.c. doses of 0.2 or 0.3 ml of iron-dextran from 11 weeks to 7.5 months. Mice injected with dextran only developed no tumours. Positive results were also obtained in mice by Haddow & Roe (1964): three groups of 20 or 30 male mice, given 87 x 0.01 ml, 47 x 0.05 ml or 30 x 0.3 ml s.c. doses of iron-dextran, developed 0, 12 (12 sarcomas) and 15 (14 sarcomas, one histiocytoma) tumours at the injection site respectively. These results suggested that there is an association between dose and response.

Negative results were, however, obtained by Pai et al. (1967). After ten once-weekly s.c. doses of 0.05, 0.1 or 0.2 ml iron-dextran to groups of ten to 18 female Swiss or XVII x C57BL hybrid mice, no local sarcomas developed in 35 mice which survived seven months or more from the start of treatment. Langvad (1968) observed only one sarcoma at the site of injection of iron-dextran (14-52 s.c. doses of 250 or 500 mg/kg bw of trivalent iron in a total of 147 mice of four strains {ST/a, DBA/2, C3H and AKR/a}). Only one sarcoma arose in a control group of 100 mice that received Tyrode's solution. When single s.c. doses of iron-dextran equivalent to 25-2500 mg/kg bw of trivalent iron were given to groups of ST/a mice of different numbers (6 to 44 males and 8 to 60 females), altogether three

local tumours (one sarcoma, two unspecified) developed in three females (1/53 on 500 mg/kg, 1/10 on 1000 mg/kg and 1/8 on 2500 mg/kg). However, an increase in the incidence of distant tumours was noted only in females (61/137 test females versus 13/60 control females), and two-thirds of these tumours were of lymphoreticular origin. Langvad (1968) suggested that iron-dextran may act as a carcinogenic factor in the case of lymphoreticular neoplasia, increasing host susceptibility to the oncogenic virus possibly present in both test and control animals.

Groups of 12-24 male and female Swiss or XVII x C57BL hybrid mice were given ten once-weekly i.m. injections of 0.1 or 0.2 ml iron-dextran from the age of about three months. A total of 28 mice survived at least seven months from the start of treatment, and one developed a fibrosarcoma at 21 months from the start of the treatment (Pai et al., 1967). Four groups of 50 stock albino mice were given once-weekly i.m. doses (0.1, 1.0, 5.0 or 10.0 mg iron) over 12 months. Only one sarcoma developed in 54 survivors at 12 months (Golberg et al., 1960); no sarcomas were seen in 79 survivors at one year after three groups of 50 mice were given ten once-weekly i.m. injections of iron-dextran at 0.1, 1.0 or 10.0 mg iron (Golberg et al., 1960).

(b) Iron-dextrin complex: Twenty male mice were given once-weekly s.c. injections of 0.05 ml iron-dextrin (1 mg iron) for 30 weeks. Local tumours developed in 3 of 12 survivors at 12 months after the first injection (Fielding, 1962).

(c) Iron-sorbitol-citric acid complex: Forty male mice were given once-weekly s.c. injections of this complex (0.02 ml containing 1 mg iron) for 30 weeks. No injection-site tumours developed in 28 mice surviving 12 months after the first injection (Fielding, 1962).

(d) Saccharated iron oxide: Local tumours (two spindle-cell sarcomas, three histiocytomas) developed in 5/20 mice that survived for up to 14 months after the first of 13 weekly s.c. injections of 0.2 ml saccharated iron oxide (Haddow & Horning, 1960).

Rat:

(a) Iron-dextran complex: Local sarcomas developed in 25/30 male rats given once-weekly s.c. injections of 1 ml iron-dextran for six months (Haddow & Horning, 1960) and in 6/10 and 5/10 rats given 46 once-weekly s.c. doses of iron-dextran equivalent to 125 or 250 mg/kg bw of iron (Langvad, 1968). In the latter experiment no tumours developed in eight controls given 46 weekly s.c. injections of 0.5 ml Tyrode's solution.

The effect of dose on local sarcoma development was reported by Roe & Carter (1967). Groups of 64, 128, 64, 32 and 16 male rats were given 0, 2, 4, 7 and 16 weekly injections of 0.75 ml iron-dextran (equivalent to 0-600 mg Fe) at the same s.c. site and observed for up to 800 days. Injection-site tumours developed in 0/64, 8/128, (five sarcomas, three fibromas), 7/64 (four sarcomas, three fibromas), 11/32 (eight sarcomas, three fibromas) and 8/16 (eight sarcomas) rats respectively, whilst a wide variety of distant tumours was seen in 5/64, 19/128, 4/64, 2/32 and 1/16 rats respectively. The latent period of local sarcoma development was independent of dose, but the incidence and grade of malignancy of tumours increased with the total dose administered. The numbers and distribution of distant tumours were not related to the total dose of iron-dextran given. The importance of dose in local sarcoma development was also reported by Haddow & Roe (1964). They gave groups of 20 or 30 male rats 90 x 0.01, 64 x 0.05, 20 x 0.5 and 30 x 1 ml doses of iron-dextran and observed one (sarcoma), three (two sarcomas, one fibroma), eight (all sarcomas) and 28 (20 sarcomas, 8 histiocytomas) injection-site tumours within minimum induction periods of 736, 478, 426 and 145 days respectively.

Another study investigated the effect of injecting iron-dextran into single and multiple sites on the development of local and distant tumours (Roe et al., 1964). Groups of 24 male rats were given 24 s.c. doses of 0.5 ml iron-dextran either at one, two, four

or six sites injected weekly in rotation and the animals observed up to two years. Rats with tumours at one or more injection sites totalled 14/22, 7/23, 12/24 and 10/23 in the one, two, four and six site groups respectively. The corresponding proportion of injection sites examined at post-mortem showed tumour formation in 14/22 (63.6%), 11/46 (23.9%), 29/96 (30.2%) and 17/138 (12.3%). No local tumours developed in untreated controls. Distant tumours were seen in 3/28, 4/22, 2/23, 3/24 and 3/23 rats injected at 0, 1, 2, 4 and 6 sites respectively; the difference in incidence of these various distant tumours between control (10.7%) and test (13%) animals was not significant. Animals injected at one site developed rapidly growing and generally more malignant local tumours than those injected at multiple sites. On the other hand the total number of injection-site tumours was higher in the groups with four or six different injection sites than in those with only one or two injection sites.

Golberg et al. (1960) observed sarcomas in 12/20 rats that survived for more than one year from the start of a series of repeated i.m. injections of iron-dextran (totalling 436 mg iron) and in 3/22 rats that survived for more than two years after an average of 116 mg iron injected into each of two injection sites over five months.

Rats were given repeated i.m. injections over four months (totalling 1250 mg iron in males and 800 mg iron in females). Local sarcomas, several of which were transplantable, developed in 13/18 rats between eight and ten months after the first injection of iron-dextran (Kren et al., 1968).

Braun & Kren (1968) reported local sarcomas in 8/14 rats surviving for 20-24 weeks after the last of 18 once-weekly i.m. injections of 1 ml iron-dextran.

Of 40 rats given weekly i.m. doses of 0.04 ml iron-dextran, 16/23 surviving 11-16 months developed sarcomas. In another test 22/24 rats given twice-weekly i.m. doses of 0.1 ml iron-dextran

progressively increasing to 0.4 ml over three months (total 9.5 ml/rat) developed sarcomas by six to eight months after treatment ceased (Richmond, 1959, 1960).

(b) Iron-dextrin complex: Two groups of 39 rats (sexes approximately equally divided) were given twice-weekly i.m. doses of iron-dextrin for four months, starting either at 0.05 ml and progressively increasing to 0.2 ml (total 255 mg/rat), or starting at 0.1 ml and increasing to 0.4 ml (total 510 mg/rat) (Lundin, 1961). Sarcomas developed in 16/31 and 25/30 animals respectively that survived for between 36-68 weeks.

(c) Iron-sorbitol-citric acid complex: Twenty-four male rats were given twice-weekly s.c. injections of 0.05 ml iron-sorbitol-citric acid complex (1 mg/50 g bw of iron) for 52 weeks, apart from three treatment-free periods when treatment had to be suspended because of toxic effects (Roe & Haddow, 1965). In all 79 injections (providing 830 mg iron) were given, and animals were observed up to 25 months of age for local and distant tumours. No injection-site tumours developed in 19 rats surviving for more than one year; six survivors showed distant tumours (four benign, two malignant) which were considered unlikely to be related to treatment. Wrba & Mohr (1968) gave twice-weekly s.c. injections of about 0.92 ml/kg of the complex (1 ml contains 50 mg trivalent iron) to 60 rats, and no injection-site tumours developed in eight rats which survived 16 months or in nine survivors out of 30 controls given similar injections of iron-free solution. Iron-sorbitol-citric acid complex was given to 28 male and 25 female rats i.m. in twice-weekly doses starting at 0.05 ml (0.25 mg iron) and progressively increasing to 0.2 ml (total dose 255 mg/rat) over four months (Lundin, 1961). One injection-site tumour (a fibroma) developed in 38 rats observed up to 68 weeks.

(d) Saccharated iron oxide: After once-weekly i.m. injections (continued throughout life) of 0.5 ml saccharated iron oxide (10 mg iron) to 12 male rats, no local tumours developed over a period of 17 months; the animals showed necrosis and recurrent ulceration at

the site of injection, but the resultant granulation tissue reaction did not progress to neoplasia (Richmond, 1959, 1960).

Hamster:

Iron-dextran complex: Of 50 Syrian hamsters given repeated s.c. injections of 0.5 ml iron-dextran weekly for ten weeks, one developed a local sarcoma after nine months. Of 32 Chinese hamsters given 0.1 or 0.3 ml weekly for seven and four months respectively, one developed a local sarcoma following repeated injections of iron-dextran (Haddow & Horning, 1960).

Rabbit:

Iron-dextran complex: Three males and three females were given 28 once-weekly i.m. injections of 2 ml iron-dextran starting at six months of age and were observed for up to four years after the first injection. Two of them developed pleomorphic sarcomas at 39 and 48 months after the first injection, and one of the sarcomas metastasized to the lungs (Haddow et al., 1964). No distant primary tumours were seen.

Squirrel monkeys:

Iron-dextran complex: Three males and three females were given seven to 40 once-weekly i.m. injections, each of 0.25 ml iron-dextran (total iron dose 500 mg/animal); five controls received similar injections of 0.25 ml physiological saline (Carter et al., 1968). No local or distant tumours were seen up to 63 weeks after the last test injection; only three of six treated animals survived 44-63 weeks after the last injection. Increased amounts of fibrous tissue were seen at the site of injection, but no tumours or preneoplastic lesions were found; however, a more prolonged experiment in this species would have been desirable.

3.2 Other relevant biological data

(a) Animals

In the rat, a high proportion of the dose remains at the site of i.m. or s.c. injection, whereas in mice, rabbits and dogs more is

translocated to the liver (Golberg et al., 1960). Following repeated i.m. injections of iron-dextran to squirrel monkeys a significant uptake of iron was seen, especially in liver, spleen and kidneys and to a lesser extent in the pancreas, lungs, adrenal glands and myocardium; iron was largely confined to macrophages and evoked little tissue reaction (Carter et al., 1968). According to Richmond (1959) dextran is rapidly split off after i.m. injection of iron-dextran, and the iron complexes with protein to form haemosiderin.

Studies in mice (s.c.) and rat (i.m.) revealed only small amounts of residual iron at the injection site of mice given repeated s.c. injections of iron-sorbitol-citric acid complex, in contrast to much greater amounts of residual iron seen following administration of iron-dextran and to even greater amounts still seen with iron-dextrin (Fielding, 1962; Lundin, 1961). Similar results were obtained in i.m.-treated rats by Lundin (1961). Other workers have found that the residual iron concentration at the site of i.m. injection in rabbits was lower when iron-sorbitol-citric acid complex was injected than for iron-dextran (Lindvall & Andersson, 1961). Despite the more rapid absorption from the injection site, the levels of iron attained in the liver, spleen and lymph nodes at four to six weeks after commencement of repeated i.m. injections of iron-sorbitol-citric acid complex in rats were lower than those obtained with iron-dextran; and the tissue levels of iron attained with iron-dextrin were lower than those obtained with either iron-dextran or iron-sorbitol-citric acid complex (Lundin, 1961). With iron-sorbitol-citric acid complex, absorption from the injection site in cats occurs predominantly by the peripheral circulation, with limited absorption by the lymphatic route (Svärd & Lindvall, 1961); whereas with the higher molecular iron-dextran absorption is primarily by the lymphatic route in rabbits (Beresford et al., 1957).

(b) Man

Iron-dextran disappeared from the injection site in man, with 60% absorption in 24 hours and 90% absorption at five days post-injection (Stevens, 1958).

About 17-45% of ^{59}Fe-labelled iron-dextran administered remained at the injection site after 20 days (Grimes & Hutt, 1957; Karlefors & Nordén, 1958). The latter workers also noted a peak plasma level at 24 hours and the presence of very little ^{59}Fe in the urine.

Following i.m. injection of 1.4-2.0 ml ^{59}Fe-labelled iron-sorbitol-citric acid complex containing 70-100 mg iron to 12 human patients with iron-deficiency anaemia or sideropenia, Pringle et al. (1962) observed a rapid disappearance of radioactivity from the injection site with no significant radioactivity being detected at ten hours after injection. Thirty-three per cent of the dose was excreted in the urine and < 1% in the faeces. Plasma levels reached a peak within two hours of dosage. Wetherley-Mein et al. (1962) also observed a rapid disappearance from the site of injection of ^{59}Fe-labelled iron-sorbitol-citric acid complex administered i.m. to three normal subjects and five iron-deficient patients.

Clearance from the injection site is more rapid with ^{59}Fe-labelled iron-sorbitol-citric acid complex (1.5 ml containing 50 mg iron) (Wetherley-Mein et al., 1962) than with iron-dextran (5 ml containing 250 mg iron) (Grimes & Hutt, 1957).

3.3 Special considerations on the carcinogenicity of iron-carbohydrate complexes in animals

With the administration of low doses of iron-dextran to animals, recovery from the initial tissue reaction is possible and no sarcomas develop; but with repeated massive doses of iron-dextran, the lymphatic absorption mechanism is overwhelmed and iron accumulates at the site of injection (Beresford et al., 1957; Golberg et al., 1960; Lane, 1964; Grasso & Golberg, 1966). At high doses there is an initial granulomatous reaction consisting of a marked macrophage response with fibroblastic proliferation. This is followed by death of macrophages and considerable local necrosis, which continues until sarcomas appear (Muir & Golberg, 1961a, b; Baker et al., 1961). Both Baker et al., (1961) and Roe (1967) regard the stage of fibroblastic proliferation as a precursor of sarcomatous change. Regarding the mechanism of tumour development, Roe (1967)

considers a physical mechanism operating as in the Oppenheimer effect to be the most plausible.

Haddow & Horning (1960) and Roe (1967) argue that since tumour induction at the site of injection is a local phenomenon it is the actual size of the dose and not its size relative to body weight that matters. In contrast, Golberg et al. (1960, 1961) and Cox (1964) emphasise that dosage must be considered in relation to the available mass of tissue at the injection site. Golberg et al. (1960, 1961) and Fielding (1962) suggest that a threshold dose exists below which no sarcomas develop. Golberg et al. (1960) consider that the doses causing sarcomas in experimental animals have little counterpart in clinical medicine. According to Fielding (1962) the dose approximating to the threshold dose in mice is 1/250th of the usual single clinical dose, or 1/40th of the human dose on a body weight basis.

It appears that the iron-carbohydrate complex per se, rather than either of its two components, is responsible for sarcoma production. Thus, tests involving repeated injections of simple iron compounds into mice proved negative (Haddow et al., 1961). Also weekly i.m. injections of 0.5 ml dextran to 12 rats over 17 months, or of 0.1-0.4 ml dextran to 12 rats over three months, failed to induce local tumours (Richmond, 1959). Similar failures were reported in 50 mice given weekly 0.2 ml doses of dextran s.c. for 11 or 16 months (Haddow & Horning, 1960) and in 70 mice given repeated injections (unspecified) of dextran (Haddow et al., 1961). Tests on dextrin in rats given twice-weekly i.m. injection for four months starting at 0.1 ml and progressively increasing to 0.4 ml also gave negative results (Lundin, 1961). However, the dextran and dextrin used in these tests were not necessarily the same as the corresponding carbohydrate component liberated in vivo during the metabolism of the iron-carbohydrate complex.

3.4 Observations in man

Since the introduction of iron-dextran to clinical practice in the 1950s, only one case of cancer has been reported as a possible complication. A 74-year-old woman developed at the site of injection an

undifferentiated soft tissue sarcoma, three years after receiving six inoculations (100 mg each) of iron-dextran for a blood-loss anaemia (Robinson et al., 1960). It is not possible to determine whether the association in this single case is causal, and no long-term observations have been made on persons receiving this drug.

Pathological studies of injection sites following usual therapeutic doses of iron-dextran have shown little or no changes (Baker et al., 1961). In two cases, massive doses produced some fibrosis and heavy accumulations of iron in macrophages but no indications of neoplasia or preneoplasia (i.e., fibroblastic proliferation).

4. Comments on Data Reported and Evaluation

4.1 Animal data

Repeated i.m. or s.c. injections of iron-dextran induced local sarcomas in the mouse, rat, rabbit and hamster; tests of relatively short duration in squirrel monkeys gave negative results. No conclusive evidence of tumour formation at sites distant from the injection site has been obtained in animals. It would appear that the carcinogenic activity of certain iron macromolecular complexes after i.m. or s.c. injections into rodents is a property of the complex itself, since neither the iron nor the carbohydrate component alone induces sarcomas. The severity of the early tissue changes at the injection site, which is increased by iron overloading, probably increases the risk of sarcoma development at that site.

Neither s.c. nor i.m. injections of iron-sorbitol-citric acid complex induce local sarcomas in rats or mice. It has been suggested that the negative results obtained with this complex are due to its more rapid removal from the injection site as compared with other iron macromolecular complexes which produce sarcomas. The Working Group noted that this compound could not be tested at higher doses than those employed, on account of the toxic effects produced.

Both iron-dextrin complex and saccharated iron oxide produce local sarcomas in mice after repeated s.c. injections. Iron-dextran also produces local sarcomas in rats after repeated i.m. injections.

4.2 Human data

Iron-dextran was first introduced for clinical use during the 1950s, and other iron macromolecular complexes intended for parenteral admininistration were introduced subsequently. A single case of sarcoma at the site of repeated injections of iron-dextran has been described, but it is not known if the sarcoma was caused by the treatment. There is no other evidence to suggest that any of these agents under conditions of clinical use constitute a risk of cancer in man. The period since the introduction of parenteral iron therapy may, however, be too brief for sarcomas to have developed. No epidemiological studies have been reported.

5. References

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CUMULATIVE INDEX TO IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISK OF CHEMICALS TO MAN

Numbers underlined indicate volume and numbers in italics indicate page.

Aflatoxin B1	1,*145*
Aflatoxin B2	1,*145*
Aflatoxin G1	1,*145*
Aflatoxin G2	1,*145*
4-Aminobiphenyl	1,*74*
Arsenic	2,*48*
Arsenic pentoxide	2,*48*
Arsenic trioxide	2,*48*
Asbestos	2,*17*
Auramine	1,*69*
Benzidine	1,*80*
Beryl	1,*18*
Beryllium	1,*17*
Beryllium oxide	1,*17*
Beryllium sulphate	1,*18*
Cadmium	2,*74*
Cadmium carbonate	2,*74*
Cadmium chloride	2,*74*
Cadmium oxide	2,*74*
Cadmium sulphate	2,*74*
Cadmium sulphide	2,*74*
Calcium arsenate	2,*48*
Calcium arsenite	2,*48*
Calcium chromate	2,*100*
Carbon tetrachloride	1,*53*
Chloroform	1,*61*
Chromic oxide	2,*100*

Chromium	2,*100*
Chromium dioxide	2,*101*
Chromium trioxide	2,*101*
Cycasin	1,*157*
Dihydrosafrole	1,*170*
3,3'-Dimethylbenzidine	1,*87*
Haematite	1,*29*
Iron-dextran complex	2,*161*
Iron-dextrin complex	2,*161*
Iron oxide	1,*29*
Iron-sorbitol-citric acid complex	2,*161*
Isosafrole	1,*169*
Lead acetate	1,*40*
Lead arsenate	1,*41*
Lead carbonate	1,*41*
Lead chromate	2,*101*
Lead phosphate	1,*42*
Lead subacetate	1,*40*
Methylazoxymethanol acetate	1,*164*
N-Methyl-N,4-dinitrosoaniline	1,*141*
Nickel	2,*126*
Nickel acetate	2,*126*
Nickel carbonate	2,*126*
Nickel carbonyl	2,*126*
Nickelocene	2,*126*
Nickel oxide	2,*126*
Nickel subsulphide	2,*126*
Nickel sulphate	2,*127*
N-[4-(5-Nitro-2-furyl)-2-thiazolyl] acetamide	1,*181*
N-Nitrosodiethylamine	1,*107*
N-Nitrosodimethylamine	1,*95*
Nitrosoethylurea	1,*135*
Nitrosomethylurea	1,*125*

Potassium arsenate	2,48
Potassium arsenite	2,49
Potassium dichromate	2,101
Saccharated iron oxide	2,161
Safrole	1,169
Sodium arsenate	2,49
Sodium arsenite	2,49
Sodium dichromate	2,102
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Tetramethyllead	2,150
o-Tolidine	1,87