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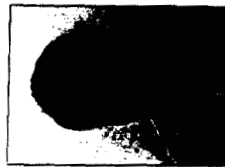
# Epidemiology and the identification of metals as human carcinogens

JOHN H. DUFFUS

*Classification of substances as probable human carcinogens under the current IARC classification scheme is dependent on epidemiological evidence. The epidemiological data relating to the four metals currently identified as probable human carcinogens, in the metallic form or in compounds, are reviewed and the weaknesses identified. These weaknesses lie mainly in exposure assessment. The weaknesses may be overcome to some extent by the use of metamorphographic methods as applied recently to the respiratory cancers that occurred at the Clydach Nickel Refinery in the first 30 years of this century. The general conclusion is that the epidemiological data relating to metals are unsatisfactory bases for the IARC classifications. There is a need to revise these classifications and to make them more precise by identifying exactly the substances which have caused human cancers.*

## Introduction

Epidemiological studies of exposed human populations are the only accepted bases for definite classification of substances as human carcinogens. There are two types of epidemiological study generally applied – the cohort study and the case/control study. A case control study requires the identification of people who have the disease of interest and a suitable comparison group; the diseased and nondiseased populations are compared with reference to exposure to the



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hypothetical causative agent to see if there is a significant correlation. In a cohort study, subsets of a defined population are identified who are, have been, or may be exposed in varying degrees to the hypothetical causative agent. Again, the epidemiologists involved look for significant associations with exposures to the agent. Case control studies are quicker and cheaper to undertake than cohort studies and may be included in cohort studies. Epidemiological studies now include DNA adducts, point mutations, chromosomal derangement and the influence of oncogenes as markers of potential carcinogenicity and this has led to coinage of the term 'molecular epidemiology'.

Classical approaches to epidemiology often suffer from the following shortcomings<sup>2</sup>:

- the healthy worker effect – where the reference group has a fundamentally different health status from the study population;
- a low response rate in the study population;
- a high turnover of the study population with selection bias operating on membership of exposed groups;
- latency between exposure and effect being longer than the study period (particularly relevant to cancer);
- little evidence of a quantitative exposure effect relationship;
- poor health effect data;
- poor exposure data;
- multiple exposures confounding the analysis of data;
- undervaluing of 'non-positive' studies.

Meta-analysis is the name given to attempts to develop a valid epidemiological analysis by bringing together the results of assorted independent and often inconclusive studies and pooling their results in an attempt to develop a more conclusive summary. Quality weighting may be applied to the studies but this does not eliminate bias or confounding. In particular, meta-analysis tends to be influenced by publication bias in favour of 'positive' studies. There are currently no universally acceptable statistical techniques to compensate for the problems identified. Serious mistakes have been made by applying meta-analysis to interpretation of small trends<sup>3</sup>.

The main problem in epidemiology is the absence of good quality exposure data. This is a particular problem in studying carcinogenicity because there may be a time lag between exposure and resultant cancer of up to 40 years. Thus, we are faced with problems of retrospective exposure assessment which is often little more than guesswork<sup>4</sup>. In addition, most exposure situations involve a wide variety

of potentially carcinogenic substances and various physical and chemical forms of any metal concerned. Thus, decisions must be made on which of the possible causative substances should be assessed<sup>5</sup>. If these decisions are wrong, subsequent conclusions may also be wrong since statistical associations may be found which are irrelevant to causation.

### *The classification of carcinogens*

The International Agency for Research on Cancer (IARC) was established 25 years ago to evaluate the carcinogenic risk of chemicals to humans and to produce monographs on individual chemicals. Sixty monographs have been published and the process of evaluation adapted by IARC is the model on which all others have been based.

A group of independent experts evaluate published data on the chemical and physical properties of the agents under review, their human exposure circumstances, relevant animal studies, *in vitro* genotoxicity investigations, and human epidemiological data. An evaluation is agreed on a four point scale ranging from 1 (proven human carcinogenic risk) through probable (2A), possible (2B) and not classifiable (3) to 'the agent is probably not carcinogenic to humans' (4).

The classification is based on the strength of the evidence and says nothing about the potency of the suspected carcinogen. The Agency does not attempt to quantify risk, probably because of the continuing debate on how exactly to carry out quantitative risk assessment for carcinogens.

Lists of carcinogens produced by different bodies do not differ greatly for the known or probable human carcinogens but the purpose of the evaluations varies, some being mainly concerned with occupational or environmental exposures and others with labelling requirements. When using different lists, it is important to take into consideration the basis for each evaluation. A change in evaluation from say 2B to 2A or from 2A to 1 (using the IARC grading system) has both legal and financial implications for industry and for employees and customers.

Of the 20 chemicals classified by IARC as Group 1 carcinogens, four are metals (beryllium, cadmium, chromium and nickel). This classification is applied to compounds of the elements as well as to the elements themselves except in the case of metallic nickel which is specifically excluded. Group 2A contains no metals but Group 1 includes metal processing industries such as iron and steel founding<sup>6</sup>. Classification of metals as Group 1 carcinogens is largely based on epidemiological associations. Thus, the quality of the relevant

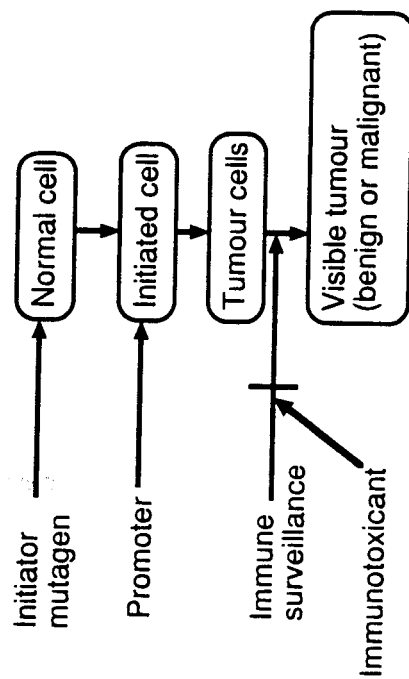


Fig. 1. Steps in the development to tumours.

epidemiology is of crucial importance and these studies must be subjected to very careful scrutiny. This scrutiny should take into account the plausibility of any proposed mechanisms of carcinogenesis. The absence of a plausible mechanism may also be a relevant consideration.

## Mechanisms of metal carcinogenesis

It has been speculated that different metals may act at various stages in the process of tumour development (Figure 1). Mutagenesis and altered gene expression in cultured cells have been attributed to exposure to chromium, nickel and cadmium but there is little evidence that this effect occurs in occupationally exposed human beings. Cadmium can interfere with calcium binding and regulation and affect intra-cellular communication and cell membrane permeability but the significance of this is uncertain<sup>7</sup>.

Metal ions are needed by the human body as essential nutrients<sup>8</sup>. The cells of modern organisms have evolved in the presence of metal ions and have adapted to them. It is likely that there are homeostatic mechanisms which must be overcome before any adverse effect such as cancer can occur. This implies the existence of thresholds for metal carcinogenicity. If this is true, it has implications for risk assessment and standard setting for permissible exposure levels.

Normal situations involve mixed exposure and interaction between metals and other substances may occur. Sometimes, simultaneous exposure to carcinogens such as polycyclic aromatic hydrocarbons may explain subsequent cancers. Rarely, if ever, have epidemiologists considered the influence of concurrent treatment with drugs on the carcinogenic effect of exposures to industrial chemicals.

Some metals, such as selenium and zinc, may act as anti-carcinogens. Oxidation state of metal ions is important in determining effects, for example, hexavalent chromium in the form of chromate is taken up by cells as chromate while trivalent chromium is not. Physical characteristics of metals and their compounds may vary in industrial processes and this may alter biological activities. Epidemiologists have generally neglected the differences in metabolism of inorganic and organic substances and any consideration of variations in physicochemical characteristics during industrial processing. Further, they have not been well served by toxicologists who have often carried out tests with inappropriate material, unrepresentative of the industrial situation, with exposures by unnatural routes, for example by injection, and have generally preferred to ignore the problem of mixed exposures<sup>9</sup>.

## Epidemiology of metals classified by IARC as probable human carcinogens (Group 2A or above)

### Beryllium

Beryllium is a low density metal which can be used with other metals to produce hard, noncorrosive, non magnetic alloys of great tensile strength. These alloys are used in aero engines, control relays, electronics and the petroleum industry. Water soluble salts of beryllium are strong electrolytes, hydrolysing to anionic linear hydroxocomplexes with liberation of hydrogen ions, resulting in highly acidic solutions.

Beryllium chloride has been reported to damage DNA and to inhibit RNA synthesis *in vitro*. Beryllium chloride induces forward mutations in bacteria and mammalian cells and sister chromatid exchanges in the latter. Beryllium sulfate is not mutagenic to bacteria or to yeast but has induced chromosomal aberrations, sister chromatid exchanges and transformation in mammalian cells<sup>10</sup>. Beryllium ions inhibit enzymes of phosphate metabolism. They also provoke a strong immune response *in vivo*. Soluble salts can cause acute beryllium disease of the lungs and the effects are dose-dependent. This may be associated with the capacity for hydrolysis referred to above and the generation of localised pH changes with high acidity referred to in the preceding paragraph. A fifth of cases may progress to chronic disease which is characterised by granuloma formation. Chronic beryllium disease is a hypersensitivity reac-

tion which seems to be linked to exposure to high temperature calcined oxide. Beryllium oxide and sulfate have been identified as causes of lung tumours in rats<sup>10</sup>.

Epidemiological studies of cancer in beryllium-exposed workers currently refer only to the US Beryllium Case Registry (of beryllium disease) and to seven US manufacturing plants. Up to 1991 there had been six studies of two US cohorts from some of these plants (4,300 workers) and the Registry data. These studies showed a 50% excess of lung cancer 15 years after first exposure, an excess which became statistically significant after 25 years. The excess was largely confined to those who had acute beryllium disease and short exposure (less than 5 years and often less than 1 year) with a two fold excess in the Registry cases. This is not good evidence for beryllium being a human carcinogen<sup>11</sup> since the excess relates best to acute dose and to acute disease, and not so well to length of exposure and to chronic (fibrotic) disease. A typical carcinogenic process relates best to chronic exposures.

The data were updated in 1991 to include women for the first time but excluding cases who were diagnosed as having lung cancer before inclusion in the Registry. The updating confirmed the observation of a two fold excess in acute beryllium disease cases and added a 50% excess in chronic cases<sup>12</sup>.

In 1993, on the basis of these studies, IARC classified beryllium as a proven human carcinogen<sup>13</sup>. However, a subsequent review<sup>14</sup> has suggested that the pre-1987 studies of two key plants are 'uninterpretable'. It may be significant that the senior author of one key paper relating to these plants resigned following public criticism of his report. The same review by Macmahon<sup>14</sup> pointed out that smoking data for the workforce are still inadequate and that the results quoted still do not show a dose response relationship.

The evidence that beryllium and its compounds cause lung cancer is very unsatisfactory. We have no other example of a situation where high dose, short-term exposure leads to a cancer not seen in lower dose, longer term exposed workers. There is a strong case for review of beryllium classification.

### Cadmium

Cadmium is used in pigments, batteries, electroplated products and as a plastic stabiliser. It is readily absorbed from the lungs and has a half life in the human of 10 years. It binds to sulfur-containing amino acids such as metallothionein. It is toxic to the kidneys and on inhalation can cause emphysema. Cadmium chloride is DNA damaging and mutagenic to bacteria. In cultured cell assay systems, it is DNA damaging, mutagenic, clastogenic and cell transforming. How-

ever, mutagenicity tests *in vivo* have been negative apart from a reported effect on mouse oocyte chromosomes. There is evidence in rats that cadmium chloride produces lung carcinoma after inhalation<sup>15</sup>.

Epidemiological studies relating cadmium to cancer apply to a relatively small number of cohorts of exposed workers, a composite group of nearly 7,000 UK workers at 17 cadmium processing plants, 3,025 workers at a UK nickel-cadmium battery plant, 606 employees of a US smelter in Colorado and 522 Swedish battery workers.

A UK study of 17 processing plants<sup>16</sup> reported an excess of lung cancer which was highest in the ever high exposure group with 10 years or more of exposure. Lung cancer was found in a UK nickel-cadmium plant to be associated with duration of high or moderate exposed employment with the excess confined to those first employed before 1947<sup>17</sup>. A small Swedish study<sup>18</sup> also found eight cases (4.1 expected) of lung cancer.

The most important cohort study relates to a smelter at Globe, Colorado which started in 1896 as a lead smelter, then became an arsenic smelter (1920-1926) and finally a cadmium smelter. There have been a number of reports on this cohort, most recently by Stayner *et al.*<sup>19</sup>. Stayner limited his study population to 606 workers employed after arsenic smelting ceased in 1926 and used occupational exposure histories obtained from company records as well as some air monitoring data. The 1993 IARC Monograph<sup>14</sup> considers the Stayner report to have the best characterised population so far studied. In the Stayner study, a statistically significant excess of lung cancer was found in non Hispanics with high exposure and the longest follow up. Various modelling techniques indicated a dose-response relationship. An attempt was made to control for smoking. These positive findings were disputed in a paper by Lamm using a case control approach although only 21 cases of lung cancer are common to both studies<sup>20</sup>.

Doll<sup>21</sup> reviewed the literature up to and including the 1992 report on the Globe smelter. The excess risk for lung cancer was usually from 10 to 50% with some excess as high as 200%. However, smoking data were limited, and the workers' exposures often included nickel and arsenic. There are also differences between studies of the same populations with respect to regional or national comparison rates for cancer and in the use of arithmetic or geometric means for the exposure data.

IARC experts classified cadmium in Group 1 in the 1993 Monograph<sup>13</sup>. Recently, Sorahan and Lancashire have studied the Globe records and in a preliminary report<sup>22</sup> pointed out that the worker records are of two types: personnel and service records,

which have limited job history data, and detailed time sheets, with different dollar rates for different jobs. Sorahan and Lancashire suggest that the time sheets are the most accurate and most detailed source of information related to worker exposure. Unfortunately, NIOSH did not use these records. In a limited comparison of the job exposure data from the two sources for 149 workers for the period April to August 1949, Sorahan and Lancashire have found notable mismatches between them. Misclassification could alter the exposure - effect relationship reported by Stayner.

### Chromium

Chromium is used for plating and for special steels. Its salts are used in dyes, paints and as tanning agents. Hexavalent chromium compounds are rapidly absorbed and excreted. They are irritant, corrosive and potent skin sensitizers. Zinc chromate is mutagenic to bacteria. In cultured mammalian cells, zinc chromate is DNA damaging, mutagenic, clastogenic and it increases the frequency of sister chromatid exchanges and induces cell transformation<sup>23</sup>. The postulated mechanism of DNA damage is shown in Figure 2. It will be noted that chromium (III) cannot enter cells and therefore is not considered to be carcinogenic. Chromium is reported to be an essential metal, involved in carbohydrate metabolism and insulin production.

IARC<sup>24</sup> reviewed chromium and chromium compounds in 1990. In the same year Langard published a thorough review of the epidemiology of chromium carcinogenicity<sup>25</sup>. For chromate producing plants in the UK and the US, a consistent excess risk for lung cancer has been reported. For chrome pigment plants in the UK and Norway, the same findings apply. Studies of chrome plating populations in the UK, US, Italy, Scandinavia and the former USSR have consistently found lung and nasal cancer excesses but they are usually small or statistically not significant. A Japanese study<sup>26</sup> of 265 workers in 40 small plating plants found that excess of lung cancer was restricted to workers with a high degree of skin ulceration or nasal perforation. Update of UK data<sup>27</sup> indicated an excess of nasal cancers in addition to confirmation of the lung cancer excess noted in earlier reports. Major process changes occurred between 1958 and 1960 and follow up of workers first employed since that time shows no excess of lung cancer.

There are four points which must be considered in relation to carcinogenicity of chromium and its compounds:

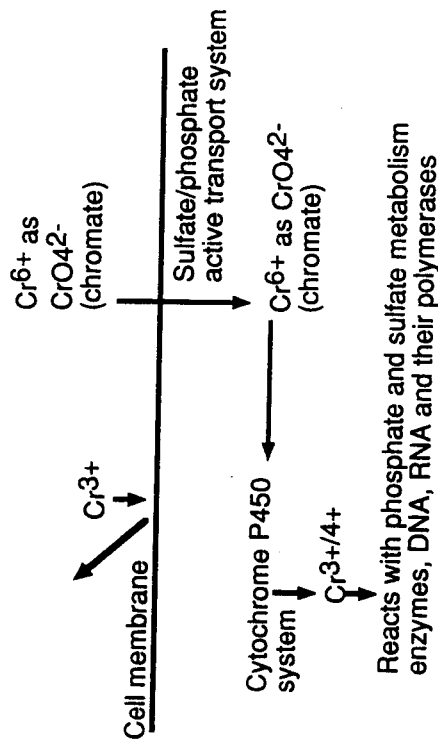


Fig. 2. Mechanism of uptake of chromium(VI) by cells and its effect on DNA.

- (1) valency - hexavalent chromium alone appears to have carcinogenic potential;
- (2) water solubility - soluble and sparingly soluble compounds are more likely to be carcinogenic than insoluble ones;
- (3) industrial process - the evidence of carcinogenicity is stronger for pigments and dichromates than it is for chrome plating;
- (4) potency - zinc chromate appears to be the most potent chromate carcinogen.

While it is generally accepted that inhalation of hexavalent chromium in the production of chromate and of chromate pigments increases the risk of respiratory cancers, it is difficult to find good evidence of an association except for zinc chromate and it may be that there are confounding factors even in this case. There is a need to look further at the exposures and respiratory cancers associated with processing of chromate and chromate pigments, perhaps applying the metamorphic techniques that have been developed in relation to the respiratory cancers associated with nickel refining (see below).

### Nickel

Nickel is used as a catalyst, in alloys, coins, magnets and batteries. It is readily absorbed, and excreted by humans and is an element essential for normal haemopoiesis. It is a potent skin sensitizer. Nickel compounds may be soluble or insoluble and this property must have an important bearing on biological effect. Nickel oxides induce

Syrian hamster embryo cell transformation as do nickel subsulfide and nickel sulfate<sup>28</sup>. However, recent studies of the carcinogenicity of nickel sulfate in rats and mice gave negative results<sup>29</sup>.

The literature on nickel carcinogenesis in exposed working populations was reviewed and updated to 1990 in the report of the International Committee on Nickel Carcinogenesis in Man (ICNCM)<sup>30</sup>. Nickel was first noted to cause lung and nasal sinus cancer over 50 years ago at the nickel refinery at Clydach in South Wales. Other reports followed from refinery populations in Canada, Norway, Germany and Russia. The consistent finding has been the high risk of lung cancer and an even higher risk for nasal cancer at the Clydach Nickel Refinery over a period of about 25 years. The ICNCM report updated nine previously studied cohorts and one case control study. The ICNCM concluded that respiratory cancer excess is mainly associated with roasting, sintering and calcining of ore and is probably linked to oxidic and sulfidic nickel compounds. They also concluded that mining and smelting operations do not carry such risks in any consistent way. The ICNCM considered that the conflicting results relating to electrolysis workers left open the question of the carcinogenic potential of soluble nickel salts. One study of metallic nickel exposure found no cancer excess and nickel alloys also seemed likely to be noncarcinogenic.

The 1990 IARC Monograph<sup>24</sup> relied heavily on the ICNCM Report for its evaluation and concluded that there is sufficient evidence of carcinogenicity in humans for nickel sulfate and for combinations of nickel sulfides and oxides encountered in the refining industry.

In 1992, updated reports on the main nickel exposed cohorts were published in book form in Nickel and Human Health<sup>31</sup>. It should be noted that, in spite of the date of publication, these reports predate the ICNCM Report. The reports concentrate on the following questions:

Which nickel compounds or processes are the cause of cancer?

What is the mechanism of nickel carcinogenesis?

Are biologically relevant routes of exposure being applied in the relevant animal studies?

What "doses" of nickel compounds are required to produce a cancer excess?

How can the occupational assessment be better standardized?

The reports covered the Clydach cohort<sup>31</sup>, as well as the Norwegian<sup>32</sup> and Canadian<sup>33</sup> cohorts. These reports had more nickel in air data

and the cohort data were more complete. Earlier excess cancer risks were confirmed but it appeared that the risk has fallen in more recently employed populations. In particular, note that the Clydach excess was shown to be confined to those employed before 1930.

With regard to nickel, the problem for epidemiologists is still which compounds, acting singly or together, or in association with others, cause the observed cancers. Recently, the application of metamorphic techniques<sup>34</sup> to a study of the 'epidemic' of respiratory cancers at the Clydach nickel refinery has cast new light on the exact cause of these cancers. Metamorphology is the name given to the use of detailed knowledge of relevant industrial processes, job descriptions, management practice, and immediate historical background of the population at risk to enable exposures to be more precisely defined. Collecting such information from many years in the past, inevitable in cancer epidemics which may have been initiated 30 years before they are recognised, is very expensive in man hours. This is why there is, at present, only one example of the metamorphic approach. In the Clydach case, there was no correlation between the throughput of Bessemer matte and cancer incidence casting doubt on the conventional attribution of carcinogenicity to nickel sulfides. Similarly, attribution of carcinogenicity to nickel oxides looked dubious in light of the continuing use of oxidic feedstock long after initiation of cancers had clearly ceased. Job sequence studies showed that the carcinogenic hazard spread through the central processing units, but was essentially confined to those units that had used calcines and the concentrates derived from them (Figure 3). When sulfuric acid heavily contaminated with arsenic was replaced by relatively pure sulfuric acid, carcinogenicity of the process was virtually eliminated. Recently, analysis of historic process samples<sup>35</sup> showed that this change correlated with the disappearance of a complex nickel arsenide from the concentrates which were bulk intermediates in the refining process. With its potential for interaction with macromolecules, and the well established carcinogenicity associated with arsenic<sup>11</sup>, it seems likely that a compound of this type is a potent carcinogen.

The metamorphic studies cited above suggest that the condemnation of nickel sulfides and oxides as carcinogens is wrong. Similar considerations of the lack of cancers associated with massive exposures to nickel sulfate at Clydach and elsewhere suggest that soluble nickel salts are not carcinogens either. This point of view is supported by the recent studies<sup>29</sup> of the carcinogenicity of nickel sulfate in rodents, which gave negative results. It seems probable that the IARC classification of nickel, "that there is sufficient evidence of

carcinogenicity in humans for nickel sulfate and for combinations of nickel sulfides and oxides encountered in the refining industry", is wrong. At the very least, there is a strong case for its revision.

## Conclusions

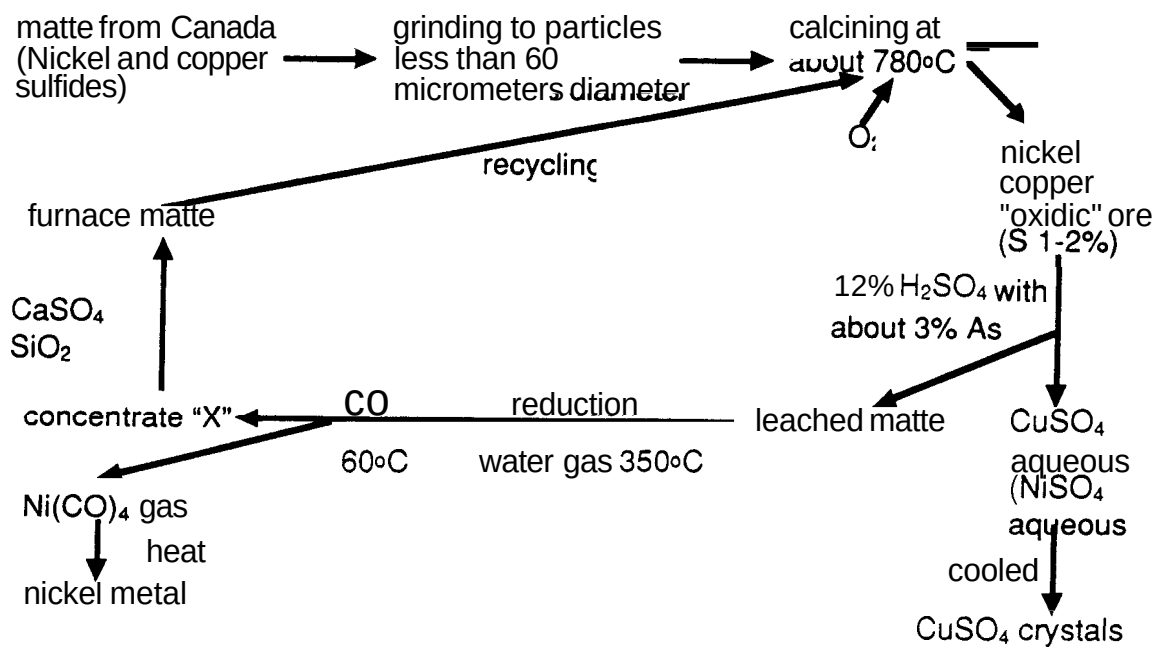
Epidemiological data bases are generally inadequate for firm conclusions to be drawn whatever the results seem to imply. Interpretation of epidemiological data may be influenced by politics, industry interest, labour union views, personal career prospects, and mistakes or misjudgements.

The four metals reviewed here, and recently, with other metals, in much more detail by Harrington<sup>36</sup>. Illustrate some of the problems in assessing human carcinogenicity from epidemiological studies. These are:

- limited data bases;
- poorly defined exposure data;
- inadequately recorded job history data;
- inability to distinguish individual compounds or processes as causative agents;
- problems of confounding exposures (especially cigarette smoking).

Techniques, such as metademography<sup>34</sup>, to improve the evaluation of past exposures are being developed. For the future, it is essential that better exposure data are obtained and samples properly archived so that future studies can generate dose-response curves. It is also essential to preserve accurate records of plant design, process methods, and work practice, including worker specific information. The tendency to use the workforce in multi-task roles makes tracing individual exposures much more difficult than in the past. Computer based monitoring may help to solve this problem. However, the rapid developments in this field have already made electronically stored records of the 1960s unavailable as the computers which can read them have been scrapped. Thus, hard copy of computer records must be kept and this again requires investment in archiving.

In interpretation of data, more attention must be paid to the plausibility of epidemiological hypotheses in terms of biochemical mechanisms. Our knowledge of bio-inorganic chemistry clearly implies that the cells of the human body have evolved to cope with the normal environmental levels of naturally occurring metal compounds which have been a factor in natural selection of cell phenotypes since life began to evolve. Novel metal compounds, especially



**Fig. 3.** The nickel refining process at the INCO refinery at Clydach, South Wales, between 1902 and 1922 when initiation of most of the respiratory cancers affecting the workforce took place.

organometallic compounds, present new problems for living organisms, but natural compounds will have their own cell homeostasis which must be overcome before any toxic effect can result. This implies a threshold, even for carcinogenic effects, and may complicate interpretation of the available data. If there is a threshold for widely occurring metal compounds, this also has consequences for regulatory decisions on permissible exposure levels.

In general, the inconclusive epidemiological evidence, the lack of plausible mechanisms, and the existence of homeostatic mechanisms for naturally occurring metals and their compounds may reasonably lead one to doubt whether many naturally occurring metals or their naturally occurring compounds can be carcinogenic under other than extreme circumstances.

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## 90 years ago

Ninety-odd years ago the essential outlines of enzymes action were becoming visible. A short while previously Kühne christened the new class of compounds - in yeast - to distinguish operator from whence it arose and, although none had been prepared synthetically, ideas on catalysis and an essentially unchanging catalyst were firmly in place. If only they had available the analytical and experimental hardward we now take for granted ...

## THE NATURE OF ENZYME ACTION

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### CATALYSIS

ALL investigators who have had occasion to consider the nature of the chemical changes taking place in living organisms must have been struck with the comparative ease with which highly stable bodies are split up under these conditions. Sugar is oxidised to carbon dioxide and water, egg-white is hydrolysed to amino-acids and other simple bodies. Under ordinary laboratory conditions, strong acids and high temperature or similar powerful agents are necessary to effect such changes. Schönbein may be mentioned as one of those who early called attention to this circumstance.

Now although, at first sight, the powers referred to may be regarded as a distinguishing characteristic of systems which are called "living," it must be remembered that there is a large and increasing class of phenomena, known to chemists as "catalytic," which manifest properties in many ways analogous. Oxygen and hydrogen, for instance, combine at ordinary temperatures so slowly that the production of water is not to be detected, and the application of the high temperature of a flame or electric spark is needed. But the presence of a minute