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A SURVEY OF TOXICITY AND CARCINOGENITY OF MINERAL DEPOSITS

University of San Francisco

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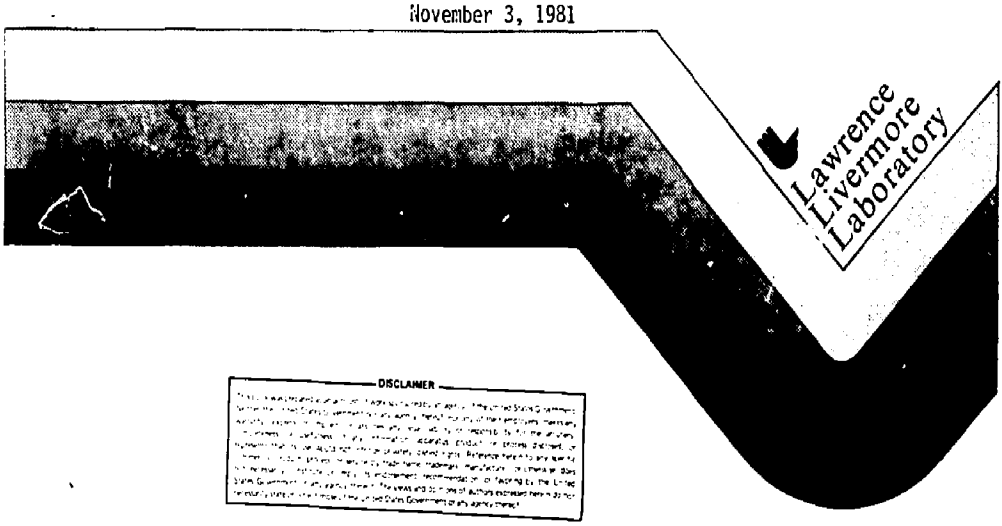

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Mineral Deposits

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A Survey of the Toxicity and Carcinogenicity of Mineral Deposits

The question of the hazard to humans and the environment is paramount in a discussion of disposal of low-level radioactive wastes. To help resolve many problems in regard to safety of disposal, it may be useful to review certain aspects of the toxic hazard of metals, which can serve as a reference point. Radioactive wastes are relatively new in the total environment; these have only been present for a few decades.

Heavy metals have been with us since the beginning of time and they have always been a natural component of the biosphere. Recently, however, with the wide scale use of metals, humans have been exposed to different concentrations and different combinations of metals.

To draw logical conclusions as to the hazard of low-level radioactive disposal, a summary of certain aspects of heavy metals, and their toxic properties are reviewed. Eventually the low-level waste problem can be compared within a framework of heavy metals.

In order to understand the extremely complex interactions of the heavy metals, one must realize that they are an integral part of the very complex cycling of elements at the earth's

surface - a schematic summary of which is given in Figure 1. Since we are dealing with the sections of the cycles where earth, air and water meet to give us the biosphere, we may also consider the metal cycles as represented by Figure 2. The situation as represented in Figure 2 is quite complex and except for a few metals, it is at best, poorly understood. Because of our lack of knowledge and the extreme complexity of the cycles, metals are usually considered singly and this may lead us in many instances to incorrect conclusions at all levels of understanding, since in nature, in the air, in the water, in the soils and in biosphere, metals do not exist and act singly, but in cohorts. This will be discussed later.

In Figure 3 is illustrated a simplified version of Figure 2 to highlight some of the main sources of metal nutrients which will act upon man in the soil-plant-animal system. However one must never lose sight of the fact that each and every interface is very complex and this is well illustrated in Figure 4.

In this survey of elements that have been known to cause toxic effects to humans we will consider only five, in any amount of detail, namely, arsenic, cadmium, chromium, lead and nickel. But before we consider some of their effects in and on the biosphere, we will outline some of their geochemical features, since a study particularly of their

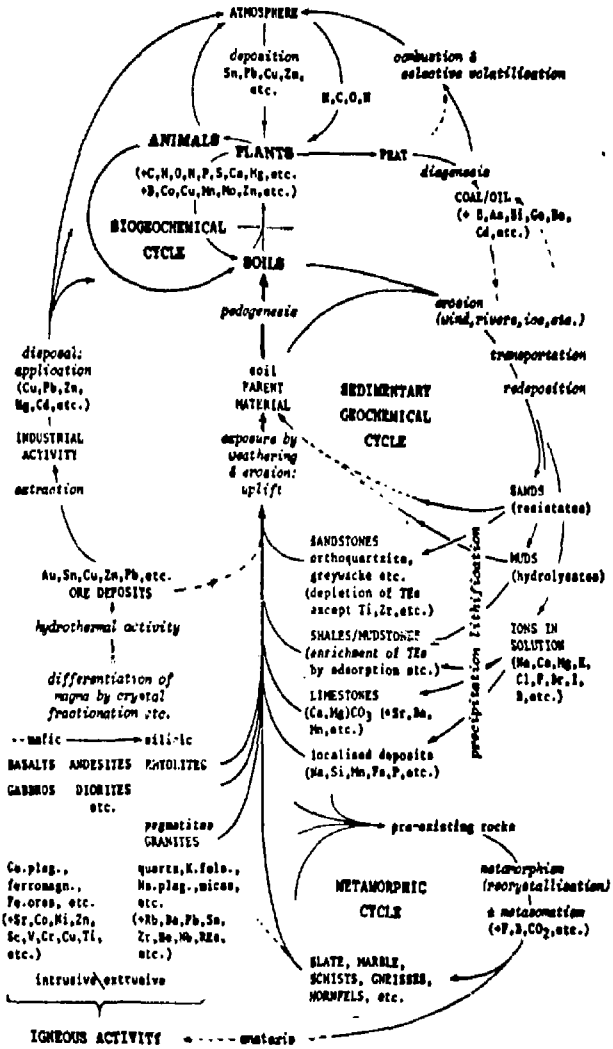


Figure 1. A schematic summary of the cycling of elements at the earth's surface

(Davies (1980))

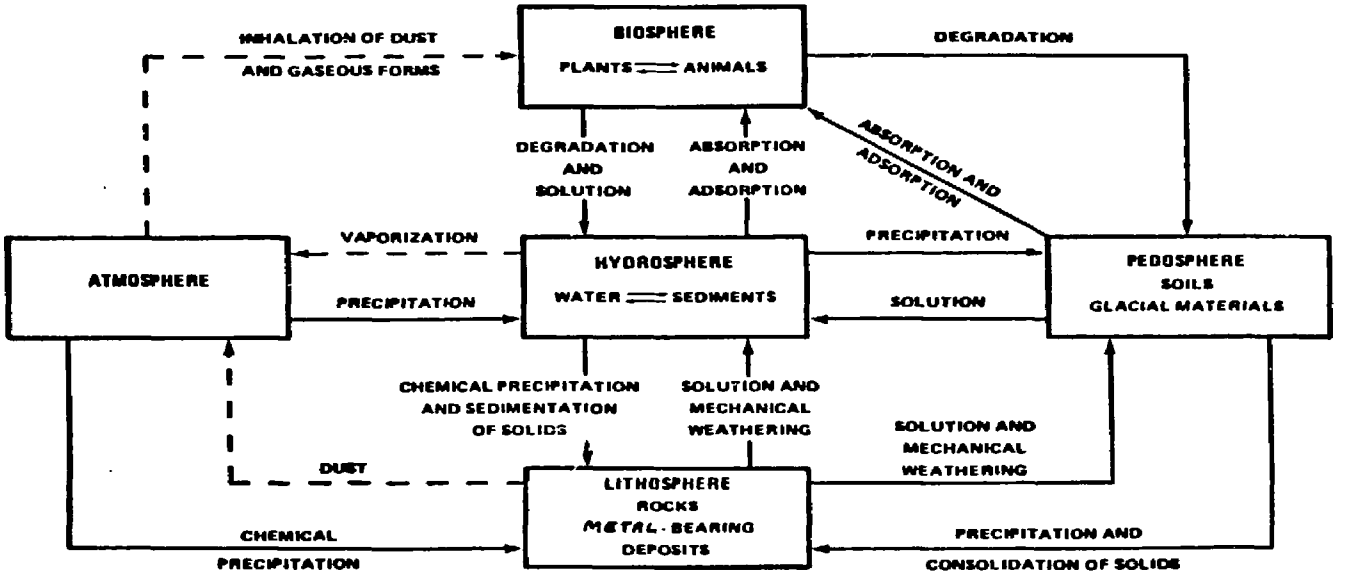


Figure 2 The generalized geochemical cycle of metals.

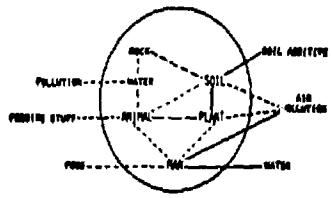


Figure 3 The soil-plant-animal system illustrating the sources of nutrient supply from within and without the immediate environmental circle.

(Mitchell (1972))

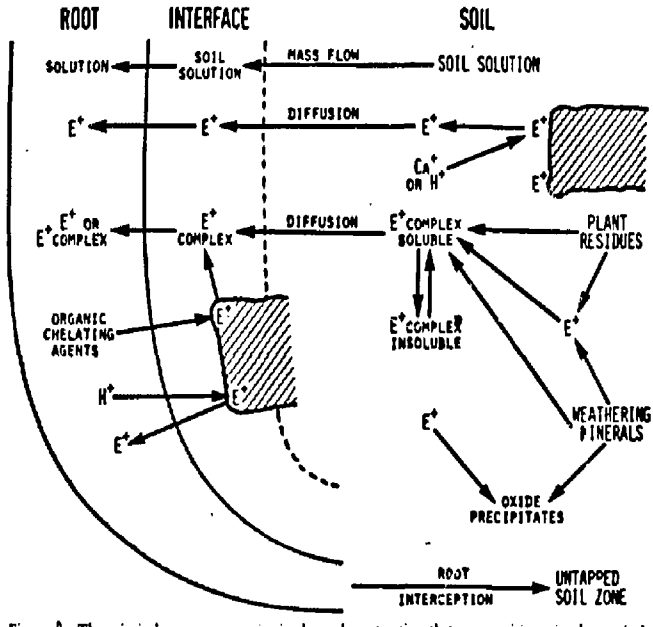


Figure 4. The principal processes operative in the transfer of trace elements from the soil to the plant root. The general symbol E^+ is used to represent any trace-element cation that can participate in the particular process illustrated. A complementary diagram could be produced to illustrate anionic processes.

(Mitchell (1972)

aqueous and soil cycles will lead us to a partial understanding of what could happen when waste is buried.

A R S E N I C

In the natural environment, four oxidation states are possible for arsenic: the -3 state, the metallic (0) state, and the +3 and +5 states. The metallic state is common for the element in certain types of mineral deposits. The +3 and +5 states are common in a variety of complex minerals and in dissolved salts in natural waters. The -3 state is present in gaseous AsH_3 (arsine) which may form under some natural conditions. The element most commonly associated with arsenic in nature is sulfur (Boyle and Jonasson 1973).

There are about 100 arsenic bearing minerals known to occur in nature. The principal arsenic minerals are arsenopyrite (FeAsS), niccolite (NiAs), cobaltite (CoAsS), tennantite ($Cu_{12}As_4S_{13}$), enargite (Cu_3AsS_4), native arsenic (As), orpiment (As_2S_3), realgar (AsS), prousite (Ag_3AsS_3), scorodite ($(Fe,Al)(AsO_4)\cdot 2H_2O$), bendantite ($PbFe_3(AsO_4)(SO_4)(OH)_6$), olivenite ($Cu_2AsO_4OH$), mimetite ($Pb_5(PO_4,AsO_4)_3Cl$), arsenolite ($As_2O_3$), erythrite ($Co_3(AsO_4)_2\cdot 8H_2O$), and annabergite ($Ni_3(AsO_4)_2\cdot 2H_2O$). Arsenic also occurs in minor quantities in practically all the common sulfides and in a great variety of secondary oxidation products, particularly in sulfates and phosphates (Boyle and Jonasson 1973). The generalized

geochemical cycles for arsenic are shown in Figures 5 and 6.

In aquatic systems, arsenic has an unusually complex chemistry, with oxidation-reduction, ligand exchange, precipitation, and adsorption reactions all taking place. Pollution control is poorly understood because of this, so Wagemann (1978) examined the typical concentrations of major and minor ionic constituents in freshwater systems in an attempt to find the possible controls on total dissolved arsenic in freshwater. He selected four metals (Ba, Cr, Fe, Ca) as possible controlling factors and studied their metal arsenates more closely in the laboratory. Barium ion, at typical freshwater concentrations, was the most likely freshwater constituent that would be capable of holding total dissolved arsenic to rather low concentrations.

There has been much discussion as to the natural concentrations of the various species of arsenic occurring in nature and their interconversion. It is now generally recognized that arsenite and arsenate interconvert via the mono- and di methylarsonic acids.

Andreae (1978) analyzed seawater from the Southern California coast and terrestrial waters from several locations in the United States for four arsenic species: arsenite, arsenate, monomethylarsonic acid, and dimethylarsinic acid. Generally,

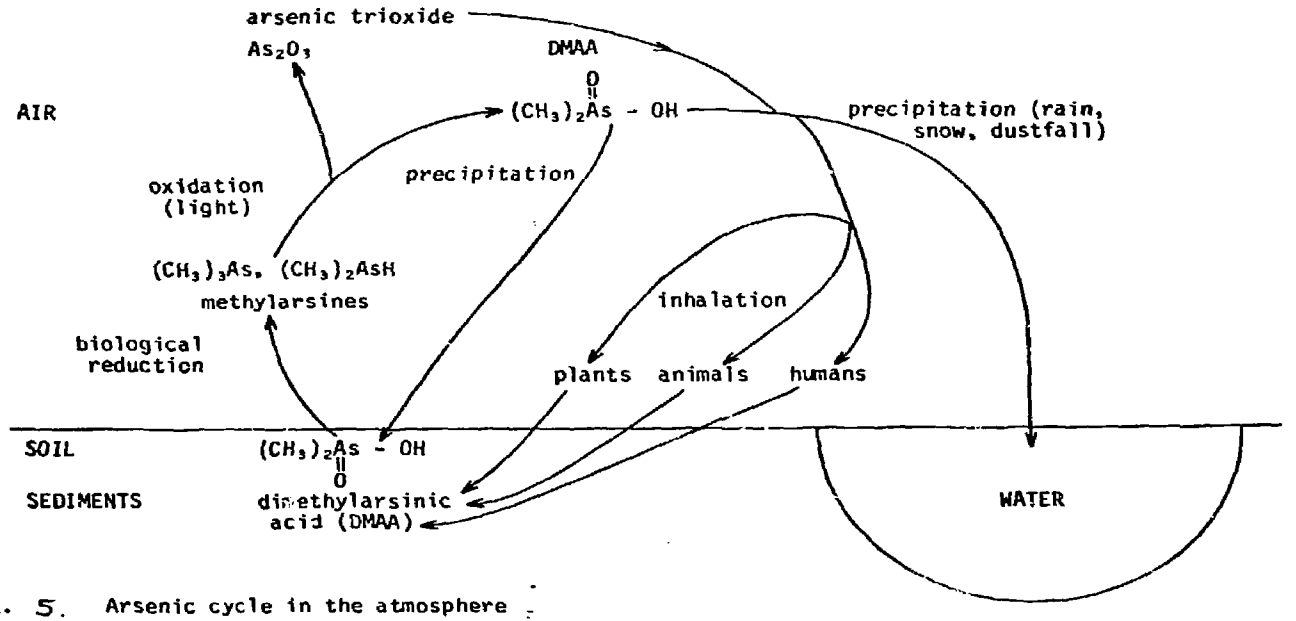


Fig. 5. Arsenic cycle in the atmosphere

(NRCC (1978))

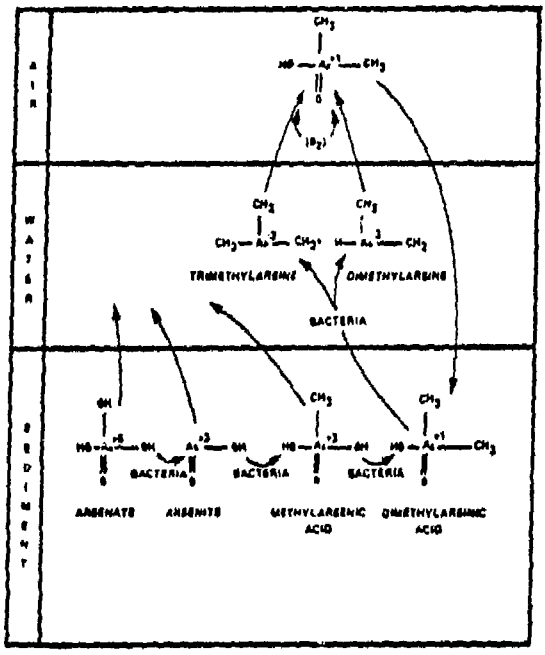


Figure 6 The biologic arsenic cycle in the aquatic environment. (Wood (1975))

arsenate was dominant. However, speciation of arsenic in natural waters is significantly influenced by biota.

These results were confirmed by the work of Waslenchuk and Windom (1978) in estuaries and Waslenchuk (1979) in rivers. Waslenchuk and Windom (1978) found that in estuaries the only detectable specie was arsenate which remained in solution as fresh and salt water mixed. Complexes occurred between arsenic and low molecular weight dissolved organic matter. These complexes presumably prevented adsorptive and coprecipitative interactions with the sediments and allowed the arsenic to travel to the ocean in a dissolved form. Arsenic which enters the estuary associated with particulates, however, apparently remained so and accumulated in the sediments.

Waslenchuk (1979) found that the levels of dissolved arsenic in rivers in the southeast of the United States are controlled by the availability of arsenic, by rainwater dilution, by the extent of complexation with dissolved organic matter, and perhaps by the metabolic activity of aquatic plants. Arsenic complexation by dissolved organic matter prevents adsorptive interactions between the arsenic and solid-phase organic and inorganic materials. The particulate arsenic load may be as important as the dissolved load with respect to material transport in rivers. It appears further

that those biologically mediated reactions which result in arsenic species disequilibria, in the ocean and lakes, have an insignificant effect on arsenic speciation in rivers.

Cycling of arsenic in the aquatic environment is dominated by adsorption and desorption to sediments. Arsenic may be sorbed onto clays, aluminum hydroxide, iron oxides, and organic material (Ferguson and Gavis 1972; Jackson et al. 1978). In some areas where phosphate minerals occur, arsenate may isomorphously substitute for phosphate (Hem 1970). Under most conditions, coprecipitation or sorption of arsenic with hydrous oxides of iron is probably the prevalent process in the removal of dissolved arsenic. In soils and underground aquifers pH is also an important factor.

Reay (1973) studied the arsenic levels in an arsenic-rich Waikato river (New Zealand), and related bioaccumulation of arsenic by aquatic plants to the total amount transported by the river. By estimating total production (ecological) and the amount of arsenic transported by the river, the author estimated that only 3-4% of the annual arsenic input to the river was bioaccumulated, with much of the balance being discharged to the sea and the remainder settling out with sediment at impoundments.

It is known that arsenic occurs naturally in high concentrations in some parts of the world for example SW Britain and some parts of Switzerland, and New Zealand. However, the long term effects upon fauna and humans appears not to have been studied to any great extent and results are inconclusive.

The global cycle of arsenic is still not clearly understood, partially due to the difficulties in obtaining accurate analytical data on arsenic content of various sections of the cycle - see for example Figure 7.

The content of arsenic in granites, basalts, limestone and sandstone is approximately 1 ppm, that in shale 13 ppm and that in soils 6 ppm. The content in seawater averages 3.7 ng As/g and in freshwater 0.5 ng As/g. The average content of plants is about 1 ppm. The amount of arsenic cycled naturally is 6 to 19 x 10^9 g/yr and that due to mining 47 x 10^9 g/yr, the latter being much larger than the former.

The bioconcentration and bioaccumulation of arsenic is not clearly understood and what data is available needs confirmation.

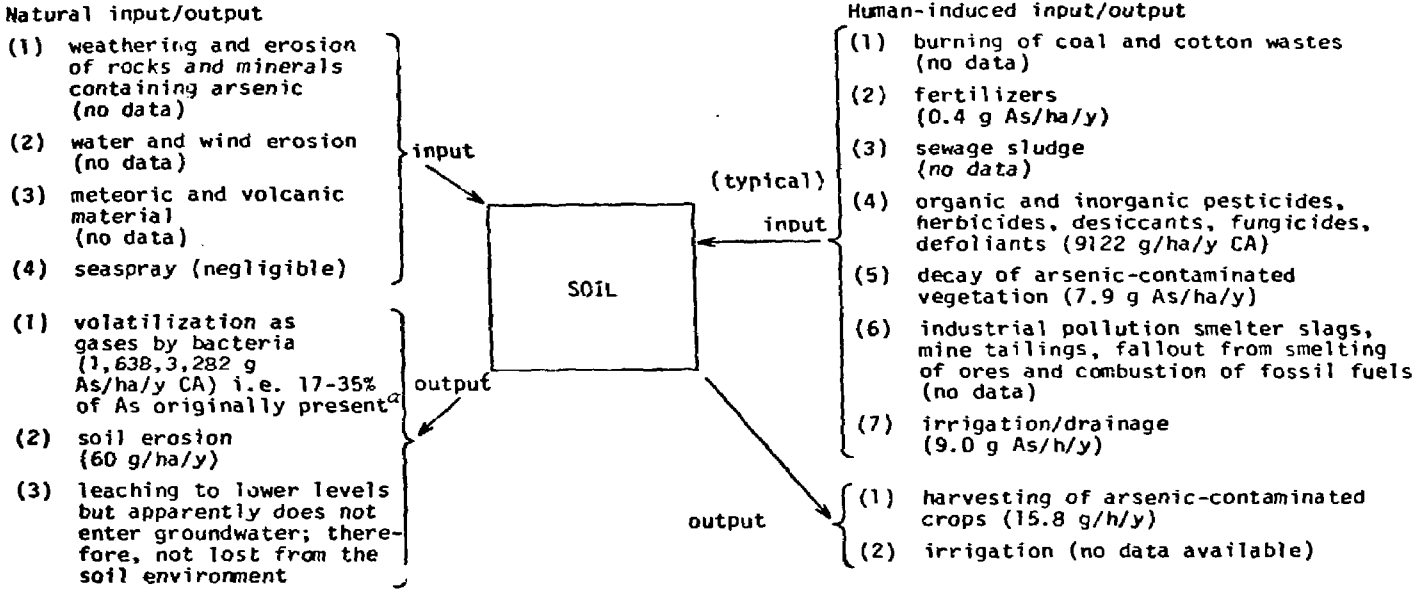


Fig. 7 Arsenic budget for soils (NRCC (1978))

C A D M I U M

During the last five years a tremendous amount of research has been done to determine just how hazardous cadmium may prove to be. In fact only lead and mercury of the trace elements have received more research attention. However, in spite of this attention we still do not know enough to accurately assess what can be done to mitigate any adverse effects if and when they occur.

Figure 8 summarizes the global cycle of cadmium as we know it today whereas, Figure 9 summarizes in more detail the atmospheric component of the cycle.

Cadmium exists in nature in the +2 form. The ionic radius of the +2 ion is estimated to be 0.97A, making it one of the larger +2 ions.

Figure 10 illustrates the interconversions which cadmium undergoes in the soil and aqueous cycles.

Cadmium is a relatively rare element that is concentrated in zinc-bearing sulfide ores (Zn/Cd ratio is usually 100 to 200) and, consequently, is found in all zinc-containing products. It is found at an average concentration of 0.15 ppm in the earth's crust. Most freshwaters contain less than 1 ppb cadmium. Cadmium levels in seawater averages about

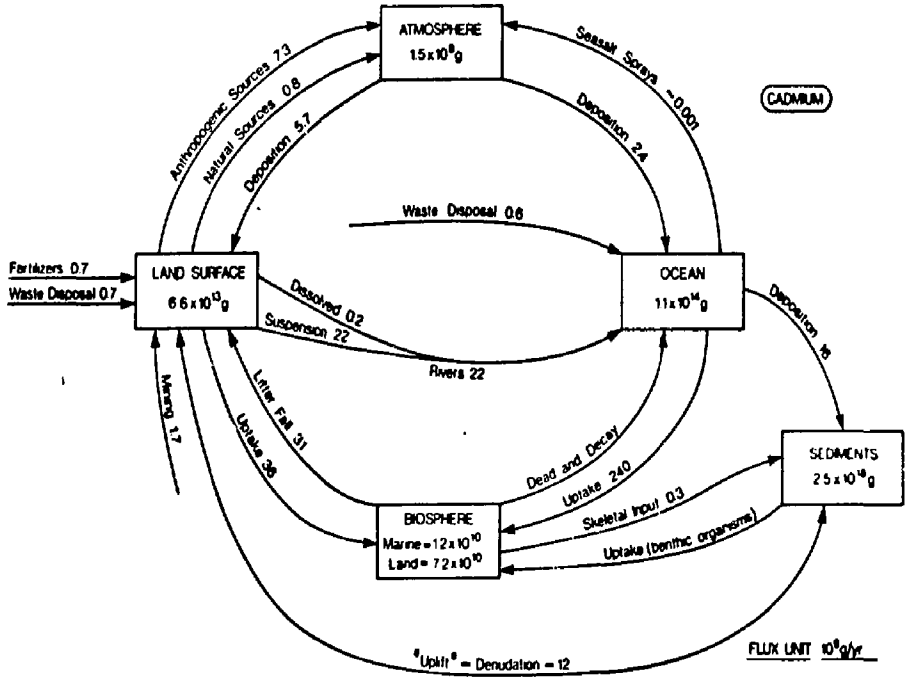


Figure 8 The global cycle of cadmium.

(Nriagu (1980a))

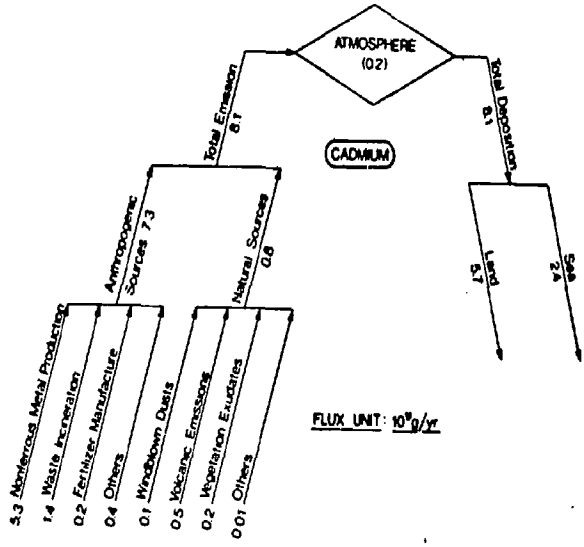
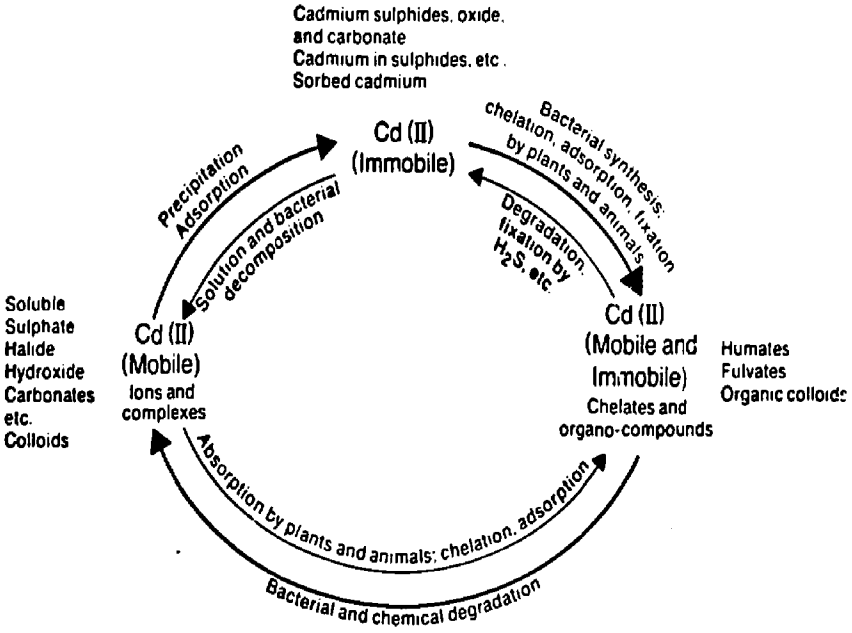


Figure 9 The atmospheric component of the global cadmium cycle.

(Nriagu (1980a))



The reaction Cd (II) $\rightleftharpoons$ Cd (O) is rare except under conditions of intense reduction.

Figure 10

Cadmium interconversions in the surficial cycle.

(NRCC (1979))

0.15 ppb. The chemistry of cadmium in surface and ground waters has been reviewed by Hem (1972).

In natural waters cadmium can be found in several chemical forms, for examples, as simple aquated ions, as metal-inorganic complexes, or as metal-organic complexes. An understanding of the chemical speciation of cadmium in any given situation can be based upon theoretical calculations of hydrolysis, oxidation/reduction and organic complexation. Cadmium forms complexes with OH^- such as $CdOH^+$, $Cd(OH)_2$(aq.), $Cd(OH)_3^-$ and $Cd(OH)_4^{2-}$. However, almost all of the soluble cadmium ions are in the divalent cation form up to about pH 9. The solubility of cadmium decreases as pH increases due to formation of solid $Cd(OH)_2$. Patterson et al. (1977) studied the removal of dissolved cadmium by hydroxide and carbonate precipitation. A comparison of experimentally determined $Cd(OH)_2$ solubility with the calculated solubility curve showed that, even at the optimal pH for precipitation, the equilibrium solubility of cadmium is still approximately 1 mg/l. Cadmium is always found in the +2 valence state in water. Therefore, redox potential has little direct effect on cadmium. Under reducing conditions and in the presence of sulfur, however, cadmium may react to form the insoluble sulfide. Under acidic conditions, CdS is more soluble. In the sediments, in anaerobic digestion of waste water, and in other reducing environments where sulfur is available, the

solubility of cadmium may be controlled by formation of CdS (Holmes et al. 1974).

Gardiner (1974), in his study of the speciation of cadmium in natural water, found that a substantial portion of the total cadmium in river and lake water will usually be present as the divalent cadmium ion, the concentration of which will be inversely related to the pH and the concentration of organic material present in the water. Humic substances usually account for most of the complexation, followed in importance by the carbonates. O'Shea and Mancy (1978), in their study of the effect of pH and hardness on cadmium speciation, found that the effect of pH and hardness was insignificant in trace metal-inorganic interactions. Hardness and pH were quite important, however, in trace metal-humic acid interactions. Increasing the pH increased the exchangeable cadmium while an increase in hardness led to a most pronounced decrease in the extent of the humic acid interaction. Metals responsible for hardness apparently inhibit the exchangeable interactions between metals and humic materials in ways that are not yet fully understood.

Guy and Chakrabarti (1976), in their study of metal-organic interactions in natural water, found that humic acids in solution and other natural complexing agents can maintain cadmium ions in a bound form at a pH as low as 3. The release

of cadmium from sediments is, therefore, apparently controlled by a combination of ion exchange and complex formation whereby the stability of the metal-organic complex determined the amount of metal solubilized.

Suzuki et al. (1979) in their study of a polluted Japanese river indicated that the organic material is mainly responsible for the accumulation of cadmium in organically polluted river sediments. These results suggest that in the transport of cadmium, suspended solids of high organic content play a dominant role in polluted waters.

Gardiner (1974) in a laboratory study found that concentration factors for mud varied between 5,000 and 50,000 depending on the type of solid, its state of subdivision, the concentration of metal ion and complexing ligands present, as well as the temperature, pH, and hardness of the water. It appeared further that humic material was at all times the major component of sediment responsible for adsorption.

In contrast, Perhac (1974) found that most of the cadmium in the bottom sediments of an unpolluted Tennessee stream was associated with carbonates and (to a lesser extent) iron oxides, and therefore hypothesized that cadmium occurs in cation lattice sites within the carbonate minerals.

Ramamoorthy and Rust (1978), in their study of Ottawa River sediments, found that, although the sediment was composed mainly of well sorted sand, it was an efficient sink for heavy metals. They discovered that this was due to the significant amount of organic material added to the sediments by the commercial use of the river for logging. Both sorption and desorption were controlled by the nature of total heavy metal loading, the sediment type and the surface water characteristics.

The adsorption of cadmium onto soils and silicon and aluminum oxides was studied by Huang et al. (1977). The results of this laboratory study indicate that adsorption is strongly pH-dependent, increasing as conditions become more alkaline. When the pH is below 6-7, cadmium is desorbed from these materials. Cadmium has considerably less affinity for the absorbents tested than do copper, zinc, and lead, and thus might be expected to be more mobile in the environment than these materials.

Another relevant observation of Huang et al. (1977) was that addition of anions to the dissolved cadmium caused an increase in adsorption. Humic acid was most effective in this regard.

Cadmium is strongly accumulated by all organisms in polluted waters. Cadmium is accumulated in the tissues of aquatic marine organisms. Fish accumulate cadmium most readily in the liver, kidneys and intestines, followed by the gills and the remainder of the body.

The influence of hardness on uptake of cadmium by a microcosm containing an alga, a rooted plant, snails, catfish, and guppies was studied by Kinkade and Erdman (1975). They found that initial uptake of cadmium was faster in hard than in soft water but that the total concentration of cadmium was greater in the organisms that were placed in soft water. The relative bioaccumulation factors descended in the following order: rooted plant > alga > guppies > snails > catfish.

Cadmium is readily accumulated through both food and water by freshwater organisms, and either source of uptake can result in the development of toxic symptoms by fishes.

Table 1 summarizes the cadmium burdens and residence times in the principal global reservoirs.

C H R O M I U M

Chromium, a transition element, occurs in nature principally as the trivalent ion Cr^{+3}, although valence states ranging from -2 to +6 have been reported. Chromium is found

Table 1 Cadmium Burdens and Residence Times in the Principal Global Reservoirs

Reservoir	Pool Mass (g)	Cadmium Concentration	Total Cadmium in Pool (g)	Residence Time (yr)
Atmosphere	5.1×10^{18} m^3	0.03 ng/m^3	1.5×10^{8}	7 days
Hydrosphere				
Oceans				
Dissolved	1.4×10^{24}	0.06 μg/kg	8.4×10^{13}	2.1×10^{4} (deep sea)
Suspended particulates (total)	1.4×10^{18}	1.0 μg/g	1.4×10^{12}	—
Particulate organic matter	7×10^{16}	4.5 μg/g	3.2×10^{11}	1.3
Fresh waters				
Dissolved	0.32×10^{20}	0.05 μg/kg	1.6×10^{9}	—
Sediments	6.5×10^{17}	0.16 μg/g	1.0×10^{11}	3.6
Glaciers	1.65×10^{22}	0.005 μg/kg	8.2×10^{10}	—
Groundwater	4×10^{18}	0.1 μg/kg	4×10^{8}	—
Sediment pore waters	3.2×10^{23}	0.2 μg/kg	6.4×10^{13}	—
Swamps an marshes, biomass	6×10^{15}	0.6 μg/g	3.6×10^{9}	—
Biosphere				
Marine plants	2×10^{14}	2.0 μg/g	4×10^{8}	18 days
Marine animals	3×10^{15}	4.0 μg/g	1.2×10^{10}	
Land plants	2.4×10^{18}	0.3 μg/g	7.2×10^{11}	20 days
Land aminals	2×10^{16}	0.3 μg/g	6×10^{9}	
Freshwater biota	2×10^{15}	3.5 μg/g	7×10^{9}	3.5
Human biomass	4×10^{9} persons	50 mg/person	2×10^{8}	1-40
Terrestrial litter	2.2×10^{18}	0.6 μg	1.3×10^{12}	42
Lithosphere (down to 45 km)	5.7×10^{25}	0.5 μg/g	2.8×10^{19}	10^{9}
Sedimentary rocks	2.5×10^{24}	1.0 μg/g	2.5×10^{18}	—
Shale and clay	1.9×10^{24}	1.3 μg/g	2.47×10^{18}	—
Limestone	0.35×10^{24}	0.08 μg/g	2.8×10^{16}	—
Sandstone	0.3×10^{24}	0.07 μg/g	2.1×10^{16}	—
Soils (to 100 cm)	3.3×10^{20}	0.2 μg/g	6.6×10^{13}	3000
Organic fraction	6.8×10^{18}	0.9 μg/g	6.1×10^{12}	>200

(Nriagu (1980a))

in concentrations of about 10-100 ppm in the crust and about 0.001-0.8 ppm in river waters. The principal chromium-bearing minerals belong to the chromite spinel group with the general formula $(Mg,Fe)O(Cr,Al,Fe)_2O_3$. Depending on the degree of substitution in the Al, Fe, Cr series, the chromites contain from 13 to 65 percent Cr_2O_3. In the environment chromium occurs most often as +3 or +6. Under most circumstances the +3 form is the preferred.

Chromite is generally resistant to chemical weathering. Due to its high specific gravity, it may be mechanically concentrated in laterites or heavy mineral placers. The chromium-bearing silicates release chromium which is then incorporated into shales and schists. Little chromium becomes solubilized, and thus, geological precipitates and evaporates have a low chromium content.

Trivalent chromium is the most stable form under redox conditions normally found in natural waters and sediments, and when in solution at pH greater than 5, quickly precipitates due to formation of the insoluble hydroxide or oxide.

Hexavalent chromium, Cr(VI), is a strong oxidizing agent, and is always found in aqueous solution as a component of a complex anion. The anionic form varies according to pH, and may be chromate (CrO_4^{-2}), hydrochromate ($HCrO_4^-$), or dichromate

($Cr_2O_7^{-2}$). Dichromate concentration is not significant unless pH values are well below those observed in most natural waters. Thus, hexavalent chromium present in most natural waters (pH>6.5) will be in the form of the chromate ion, Cr_4^{-2}. All of the anionic forms are quite soluble, and are thus quite mobile in the aquatic environment (Towill et al. 1978).

Schroeder and Lee (1975), in a laboratory study on the transformation of chromium in natural waters, found that Cr(III) and Cr(VI) are readily interconvertible under natural conditions. Their results indicated that Cr(VI) can be reduced by Fe(II), dissolved sulfides, and certain organic compounds with sulfhydryl groups, while Cr(III) can be oxidized by a large excess of MnO_2 and at a slower rate by O_2 under natural water conditions. Moreover, if aquatic conditions favor Cr(VI), then chromium will accumulate as soluble forms in waters; if, however, Cr(III) is favored, then the accumulation will occur in the sediments.

The environmental accumulation of Cr(+3) in the sediments can be explained by the hydrolysis of Cr(+3) complexes to insoluble hydroxide forms, especially $Cr(OH)_3$.

Hexavalent chromium is not absorbed to any significant degree by clays, ferric hydroxide or ferric and manganese oxides (Kharkar et al. 1968). Cr(+6) may however have some

affinity for organic materials in natural waters. It appears that while Cr(+3) is only weakly absorbed onto inorganic solids, it is adsorbed more strongly than Cr(+6), but the sorption of Cr(+3) may be ancillary to precipitation of $Cr(OH)_3$.

Chromium is accumulated in aquatic and marine biota to levels much higher than in ambient water. Levels in biota, however, are usually lower than levels in the sediments.

Namminga and Wilhmn (1977) studied heavy metal partitioning between water, sediments, and chironomid larvae (a benthic invertebrate). They found an average chromium concentration of 1.1 μ g/l in water, 7.64 μ g/g in sediments and 2.96 μ g/g in chironomids. Bioconcentration factors for chironomids to water are thus about 3,000, and for chironomids to sediments, about 0.39. Rehwoldt et al. (1975) found similar relationships among water, sediments, and biota in the Danube River.

Baptist and Lewis (1969) studied the transfer of radiolabeled Cr(+3) in an estuarine food chain consisting of phytoplankton, brine shrimp, post-larval fish, and mummichog. In general, the food chain was a more efficient pathway for uptake of chromium than direct uptake from seawater.

Distribution of chromium in water, sediment, seston suspended abiotic and biotic material), phytoplankton, mollusks, annelids, and fish in Narragansett Bay, R. I., was studied by Phelps et al. (1975). The highest concentrations of chromium were found in the sediments, followed by the seston. Phytoplankton concentrated chromium to a greater extent than other organisms, with the lowest levels being found in bottom-feeding fish.

The biogeochemical cycling of chromium as far as known is summarized in Figure 11. It should be noted that total chromium is usually measured, hence it is often difficult to know the percentages of Cr(+3) and Cr(+6) occurring naturally.

L E A D

Although the amount of research which has been done upon lead is enormous, much remains to be learnt. Figure 12 summarizes the fluxes of lead in the biogeosphere whereas Figure 13 differentiates between natural and man-made sources of these lead fluxes. The average abundance of lead in the earth's crust is approximately 15 ppm, which is equivalent to one-half ounce of lead per ton of rock. Lead is a naturally occurring element and is a major constituent of more than 200 identified minerals. Most of these are very rare, and only three are found in sufficient abundance to form mineable deposits: galena (PbS) the simple sulfide, angelesite ($PbSO_4$) the sulfate, and

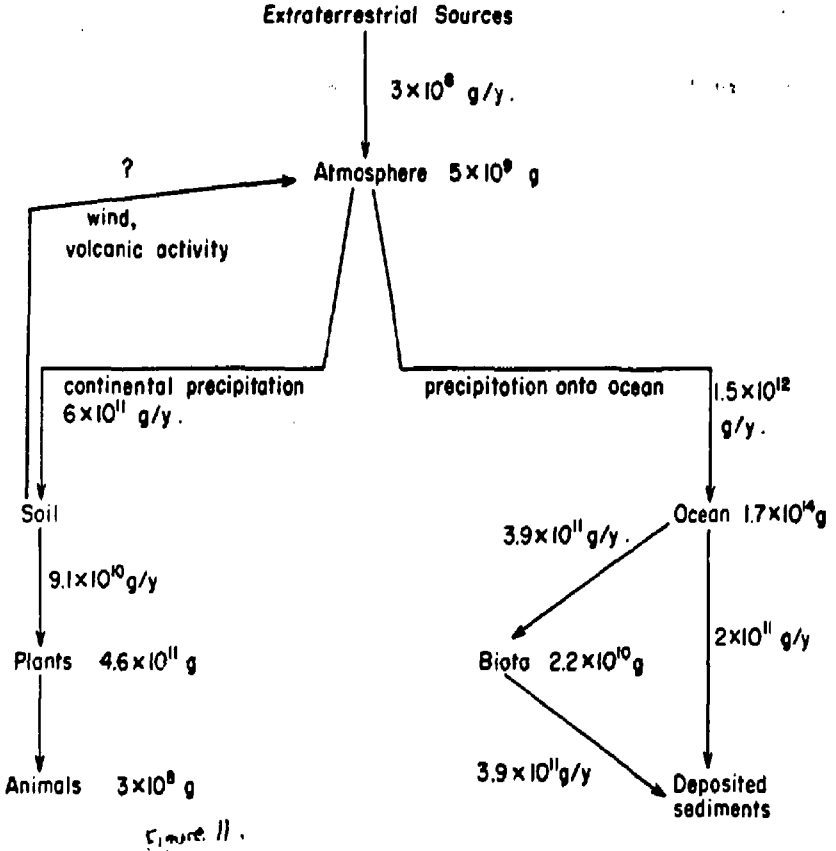
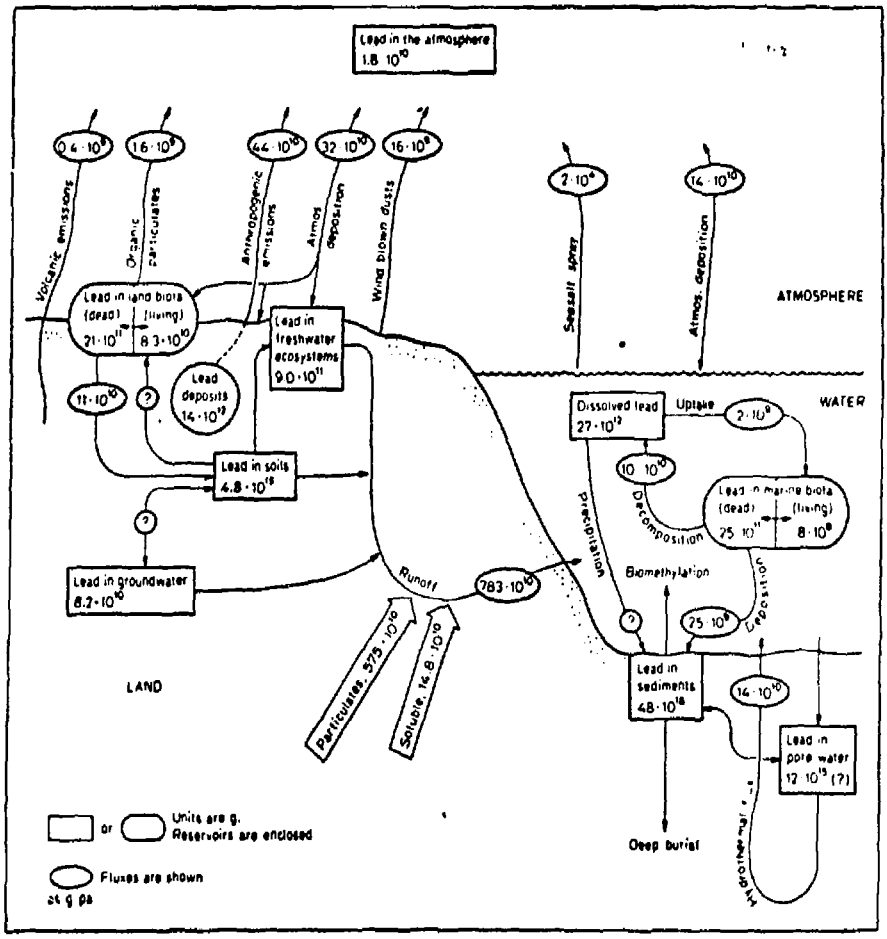


Figure 11.

Natural biogeochemical cycling of chromium.

(NRCC (1976))

Figure 12



(Nriagu (1978))

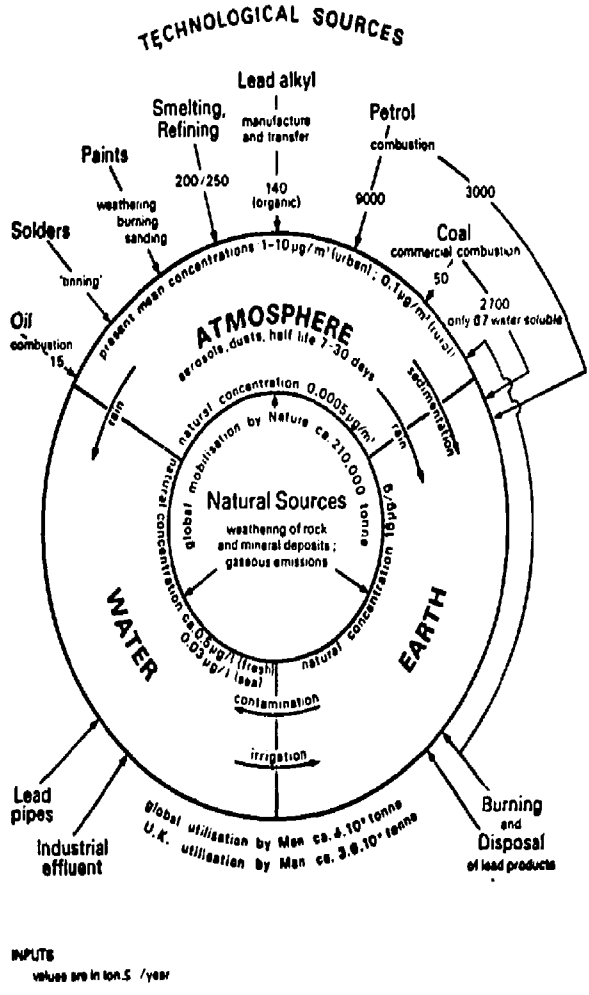


Fig. 13 Sources of lead in the ecosystem
(NRCC (1978))

cerrusite ($PbCO_3$) the carbonate. By far the most abundant is galena which is the primary constituent of the sulfide ore deposits from which most lead is presently mined. Lead ore is commonly present together with ores of copper, zinc, silver, arsenic, and antimony in complex vein deposits, but lead ore also may occur in a variety of igneous, metamorphic, and sedimentary rocks.

The tendency for lead to form complexes with naturally occurring organic materials (e.g., humic and fulvic acids) increases its adsorptive affinity for clays and other mineral surfaces. However, natural compounds of lead are not usually mobile in normal ground or surface water because the lead leached from ores becomes adsorbed by ferric hydroxide or tends to combine with carbonate or sulfate ions to form insoluble compounds (Hem 1976a).

An outstanding characteristic of lead is its tendency to form complexes of low solubility with the major anions of natural environmental systems. The hydroxide, carbonate, sulfide, and (more rarely) the sulfate of lead may act as solubility controls. Throughout most of the natural environment, the divalent form, Pb^{+2}, is the stable ionic species of lead. The more oxidized solid PbO_2, in which lead has a +4 charge, is stable only under highly oxidizing conditions, and probably has very little significance in the aquatic environment. If

sulfur activity is very low, metallic lead can be a stable phase in alkaline or near neutral reducing conditions.

Hem (1976b) calculated the fields of stability for solid species of lead based on the available thermodynamic data. Although his figures are useful in depicting equilibrium behavior, they are limited in that they do not take into account environmental interactions with organic compounds and other trace elements and, therefore, may be misleading with respect to fate and transport in normal surface waters. Hem (1976a) also modelled the equilibrium distribution between lead in solution and lead adsorbed on cation exchange sites in sediments. In general, this model suggests that in most natural environments, sorption processes would more effectively scavenge dissolved lead then precipitation.

Lead exists mainly as the divalent cation in most unpolluted waters and become sorbed into particulate phases, organic material in polluted waters will have a great effect on the chemical form in which lead will be present.

Sorption processes appear to exert a dominant effect on the distribution of lead in the environment. Several investigators have reported that in aquatic and estuarine systems, lead is removed to the bed sediments in close proximity to its source, apparently due to sorption onto the sediments

(Helz et al. 1975; Valiela et al. 1974). Different sorption mechanisms have been invoked by different investigators, and the relative importance of these mechanisms varies widely with such parameters as geological setting, pH, Eh, availability of ligands, dissolved and particulate iron concentration, salinity, composition of suspended and bed sediments, and initial lead concentration.

The adsorption of lead to soils and oxides was studied by Huang et al. (1977). The data indicate that adsorption is highly pH-dependent, but above pH 7, essentially all of the lead is in the solid phase. It should be noted that at low pH, lead is negatively sorbed (repelled from the adsorbent surface). The addition of organic complexing agents increased the affinity for adsorption. Therefore, the tendency for lead to be adsorbed probably reflects the fact that lead is strongly complexed by organic materials in the aquatic environment (Ramamoorthy and Kushner 1975).

Sorption processes appear to be effective in reducing dissolved lead levels and result in enrichment of bed sediments. It appears that, under most condition, adsorption to clay and other mineral surfaces, coprecipitation/sorption by hydrous iron oxides, and incorporation into cationic lattice sites in crystalline sediments are the important sorption processes.

Several authors, notably Jenne (1968), Lee (1975), and Hohl and Stumm (1976), have hypothesized that the sorption of heavy metals by hydrous iron and manganese oxides is a major control on the mobility of these pollutants in the aquatic environment.

Bioconcentration of lead has been demonstrated for a variety of organisms.

Microcosm studies indicate that lead is not biomagnified. Lu et al. (1975) studied the fate of lead in three ecosystems differing only their soil substrate. The ecosystems contained algae, snails, mosquito larvae, mosquito fish, and microorganisms. Lead was concentrated most by the mosquito larvae and least by the fish. Body burdens and aqueous lead concentration appeared to be strongly correlated to the percentage of organic matter and cation exchange capacity of the soils, indicating that the availability of lead in the systems was controlled by adsorption to the soils. Since pH was the same for all three soils, precipitation/dissolution of inorganically bound lead was probably not responsible for the differences in lead availability and uptake.

Merlini and Pozzi (1977a) measured lead uptake in pumpkinseed sunfish (Leponis giblosus) exposed to ^{203}Pb at pH 6 0 and 7.5. Fish at pH 6.0 accumulated three times as much lead

as fish kept at pH 7.5. Gill, liver, and fin accumulated the most lead and muscle the least. The authors attributed the increased lead uptake at low pH to the increasing concentration of divalent lead with decreasing pH. In another experiment, Merlini and Pozzi (1977b) found a direct correlation between lead accumulation by pumpkinseed sunfish and the concentration of ionic lead in water at various concentrations of total lead. Results suggest that the conditions existing in the majority of natural waters render most lead unavailable for accumulation by aquatic animals.

Patrick and Loutit (1976) studied uptake of lead by benthic bacteria and subsequent transfer to tubificid worms. The concentration factor for bacteria was approximately 360. Concentration of lead by tubificids was 0.77 times the amount fed them in the bacteria, indicating that the tubificids can clear lead more easily than the bacteria. The fact that the bacteria could concentrate lead indicates that lead in the sediments can be remobilized by bioaccumulation.

Based upon available information, fish accumulate very little lead in edible tissues; however, oysters and mussels are capable of accumulating high levels of lead. Decreasing pH increased the availability of divalent lead. Lead can be methylated by microorganisms present in lake sediments. The volatile compound resulting from biomethylation, i.e., tetra-

methyl lead, probably leaves the sediments and is either oxidized in the water column or enters the atmosphere. Biomethylation represents a process which enables lead in the bed sediments to be reintroduced to the aqueous or atmospheric environment.

N I C K E L

The global cycling of nickel has been summarized in Figure 14 whereas Figure 15 details the atmospheric portion of this global cycle. Similar data has been listed in Table 2, but with a different emphasis. Table 3 inventories the nickel content of the various components of the earth's crust, whereas Table 4 lists the nickel concentrations and the flux rates along the major pathways of the global cycle.

Nickel is a naturally occurring element and is found in the earth's crust in average concentrations of 80 ppm. Nickel is divalent in its compounds which are predominantly ionic in character.

Nickel is siderophilic and will alloy itself with metallic iron whenever such a phase is present. Nickel is only slightly miscible in iron and the two phases separate at low temperatures. The earth's core is thought to be a nickel-iron alloy with a Fe/Ni ratio of about 11:1. The weathering of nickel-rich bedrock gives rise to iron-, nickel-, and silica-rich

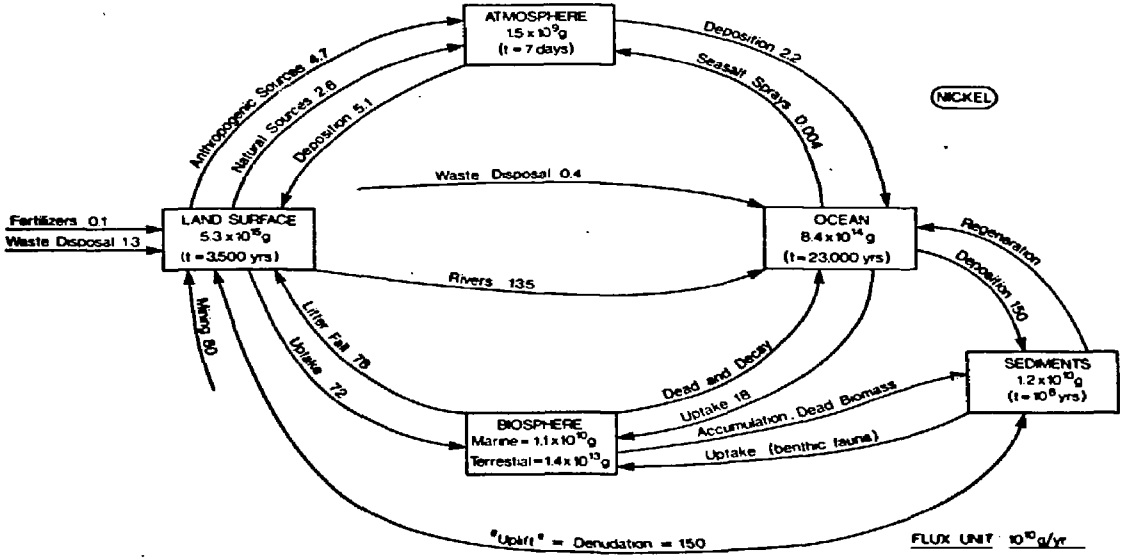


Figure 14 The global cycle of nickel on a 1-year time frame.

(Nriagu (1980 b))

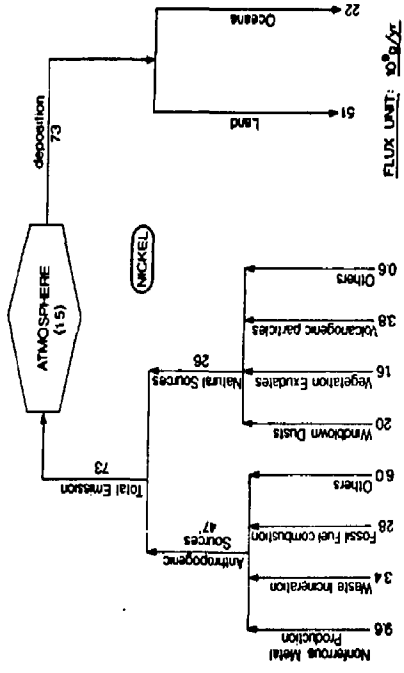


Figure 15 Atmospheric portion of the global nickel cycle.

(Nriagu, 1980b)

Table 2 Global Emissions of Air Particulates by Major Natural and Man-Made Sources

Source	Emissions (10^9 kg/year)
Natural	
Soil dust	200–500
Gas-particle conversion	900
Photochemical (from hydrocarbons)	200
Volcanoes	4–25
Forest fires	3–5
Meteoric dust	0.0036
Sea salt	1000
Man-made	
Particulate emissions	30–90
Gas-particle conversion	200–250
Photochemical (from hydrocarbons)	15

(Ntiagu (1980b))

Table 3 Inventory of Nickel in the Earth's Crust

Reservoir	Total mass (g)	Average Concentration (μg/g)	Ni reservoir (g)
Lithosphere (down to 45 km)	57×10^{24}	75	43×10^{20}
Sedimentary rocks	2.5×10^{24}	48	1.2×10^{20}
Shale and clay	1.8×10^{24}	60	1.1×10^{20}
Limestone	0.35×10^{24}	10	0.04×10^{20}
Sandstone	0.28×10^{24}	25	0.07×10^{20}
Soils (to 100 cm)	3.3×10^{20}	16	5.3×10^{15}
Organic fraction	6.8×10^{18}	70	4.8×10^{14}
Fossil fuel deposits			
Coal	10×10^{18}	15	1.5×10^{14}
Oil shale	46×10^{18}	30	1.4×10^{15}
Crude oil	0.23×10^{18}	10	2.3×10^{12}
Nickel ore reserves	–		1.6×10^{14}
Terrestrial biomass			
Plants	2.4×10^{18}	6	1.4×10^{13}
Animals	2×10^{16}	2.5	5×10^{10}
Litter	2.2×10^{18}	15	3.3×10^{13}
Oceanic			
Dissolved	1.4×10^{24}	0.6 μg/kg	8.4×10^{14}
Plants	2×10^{14}	2.5	5×10^{8}
Consumers/reducers	3×10^{15}	3.5	1.1×10^{10}
Suspended particulates	7×10^{16}	95	6.6×10^{12}
Swamps and marshes, biomass	6×10^{15}	7	4.2×10^{10}
Lakes and rivers			
Total burden	0.34×10^{20}	1.0 μg/kg	3.4×10^{10}
Planktons	5.7×10^{13}	4	2.3×10^{8}
Atmosphere	5.1×10^{18} m^3	0.3	1.5×10^{9}

(Nriagu (1980b))

Table 4 Flux Rates for Nickel along Major Pathways of the Global Cycle

	Material Flux (g/year)	Average Ni Concn. (μg/g)	Annual Ni flux (g)
Rivers			
Dissolved load	0.32×10^{20}	0.00035	1.1×10^{10}
Particulate load	1.5×10^{16}	90	135×10^{10}
Biological uptake			
Freshwaters	1.0×10^{15}	4.0	0.4×10^{10}
Oceans	6×10^{16}	3.0	18×10^{10}
Continents	12×10^{16}	6.0	72×10^{10}
Atmospheric fallout			
Lands	—	—	5.5×10^{10}
Oceans	—	—	2.4×10^{10}
Accumulation in sediments	—	—	$>1.5 \times 10^{12}$
Waste disposal			
Lands, sewage	2.1×10^{13}	150	0.38×10^{10}
Lands, fly ash	2.8×10^{14}	35	0.98×10^{10}
Oceans	25×10^{12}	150	0.38×10^{10}
Continental denudation	2×10^{16}	75	1.5×10^{12}
Fertilizers	94×10^{12}	10	0.1×10^{10}
Litter fall	5.2×10^{14}	15	78×10^{10}

(Nriagu (1980b))

solutions. Ionic nickel is very stable in aqueous solutions and is capable of migration over long distances. The high affinity of nickel for sulfur accounts for its occurrence in magmatic or metamorphic segregates of sulfide bodies. These sulfide segregates constitute the large nickel ore body at Sudbury, Ontario, which provides the world's largest mining production of nickel.

Nickel is divalent in aquatic systems. Under reducing conditions and in the presence of sulfur, the insoluble sulfide is formed. Under aerobic conditions and pH below 9, the compounds nickel forms with hydroxide, carbonate, sulfate, and naturally occurring organic ligands are sufficiently soluble to maintain aqueous Ni^{+2} concentrations above 10^{-6}M (60µg/1). Above pH 9, precipitation of the hydroxide or carbonate exhibits some control on nickel mobility.

Hydrolysis of aqueous nickel to the hydroxide, $Ni(OH)_2$, is significant only under basic conditions. Patterson et al. (1977) compared the precipitation behavior of nickel carbonate and nickel hydroxide in the context of treatment of nickel-bearing waste effluents. Although precipitation as the hydroxide was found to be the more efficient treatment, the lowest nickel concentration attained at pH values below 9 was 15 mg/1. This level is quite high with regard to its toxicity and indicates that precipitation is not an effective control on nickel

under most conditions.

In natural waters humic acids alter the solubility and precipitation behavior of nickel. Rashid and Leonard (1973) exposed nickel carbonate to humic acid and found that complexation with humic acid solubilized much of the nickel. Sorption of nickel by hydrous iron and manganese oxides and organic material probably exerts the major control on the mobility of nickel in the aquatic environment. Nickel, however, is a highly mobile metal and is sorbed only to a small extent. Lee (1975) presented cogent evidence for the importance of hydrous iron and manganese oxides in controlling nickel concentrations in aquatic environments.

However, Perhac (1972, 1974) found that almost all of the nickel transported by two Tennessee streams was in the dissolved form. The reason for this discrepancy is probably the fact that about 90% of the solids in the streams studied by Perhac were dissolved solids, so that there were very few suspended particles available for coprecipitation/sorption reactions.

The partitioning of nickel into dissolved and particulate fractions is undoubtedly related to the abundance of suspended material, competition with organic material, and concentrations of iron and manganese.

Suspended organic matter may be a good adsorbent for nickel. Rashid (1974) used colloidal humic substances to adsorb nickel and found that of the nickel thus bound, only 26% could be extracted by ammonium acetate.

Nickel is bioaccumulated by some aquatic organisms, but most concentration factors are less than 10^3. Tong (1974) showed that nickel does not bioaccumulate in lake trout, Salvelinus namaycush. In a study of the accumulation of iron, zinc, lead, copper, and nickel by algae collected near a zinc smelting plant, it was found that nickel exhibited the lowest concentration factor for all metals tested (Trollope and Evans 1976). In general, nickel is not accumulated in significant amounts by aquatic organisms.

A study of the effects of metals in aqueous and soil media is of utmost importance when considering what may happen when wastes are buried near surface or underground aquifers. As can be seen from the brief survey above, we really know very little about what the long term effects could be, either for the metals singly or what happens in actual fact - when a multitude of metals are buried, often with little thought to the long term interactions of these metals whereas it is important to understand the biogeochemical cycling of trace elements which may occur in the soil and water, since the trace elements can and do migrate from

the burial dumps into the surrounding soils and aquifers, it is equally important to understand the agricultural and the food animal trace element cycles and how these are also linked to the soil and aqueous cycles as well as to the human trace element cycle.

Plants obtain minerals from the soil and from ground water by absorption or by an ion-exchange mechanism. Most plants, like mammals, have no inherent mechanism for selectively absorbing needed elements and excluding toxic ones. The absorption of elements by plants depends largely upon the species, however even within species, plants have varying ability to concentrate heavy metals and varying ability to distribute metals within the plants. For many plants, the tissues have a lower concentration of trace elements than do seeds.

The availability of the minerals to plants is also dependent upon the chemical form of the compound, the pH of the soil and the nature of the complexing property of the organic materials in the soil.

The degree of fertilization and the nature of impurities in the fertilizer may also play a role in the amount and kind of accessory elements to which the plants are exposed, and hence which they accumulate. The term accumulate is used

as "certain plants take up the particular element in quantities very far above, sometimes many thousand times above, the average quantity for 'normal' plants."

It should be noted also that air pollution, particularly in the form of particulates, can effect the concentration of trace elements (e.g. lead) in plants via leaf uptake as well as deposition, first onto the soil and then plant root uptake.

Figure 16 illustrates one of the few fully documented cases where soil, plant, and fauna concentrations of a number of trace elements are interrelated.

When considering the effects of trace elements on humans one should remember that humans inhale air and particulates and that they ingest particulates, water (and/or liquids) and foods (both vegetable and animal). Figure 17 reminds one that although a given population is exposed to an average concentration of metal, each person receives an individual exposure (perhaps they eat more food or drink more beer) and they retain an individual amount (due to individual body conditions). If retained the element is then transported into a tissue in the body, which may or may not be the tissue where it reacts and is retained at the cellular and subcellular levels. In Figure 18 are listed some of the factors which may influence the various steps considered in Figure 17.

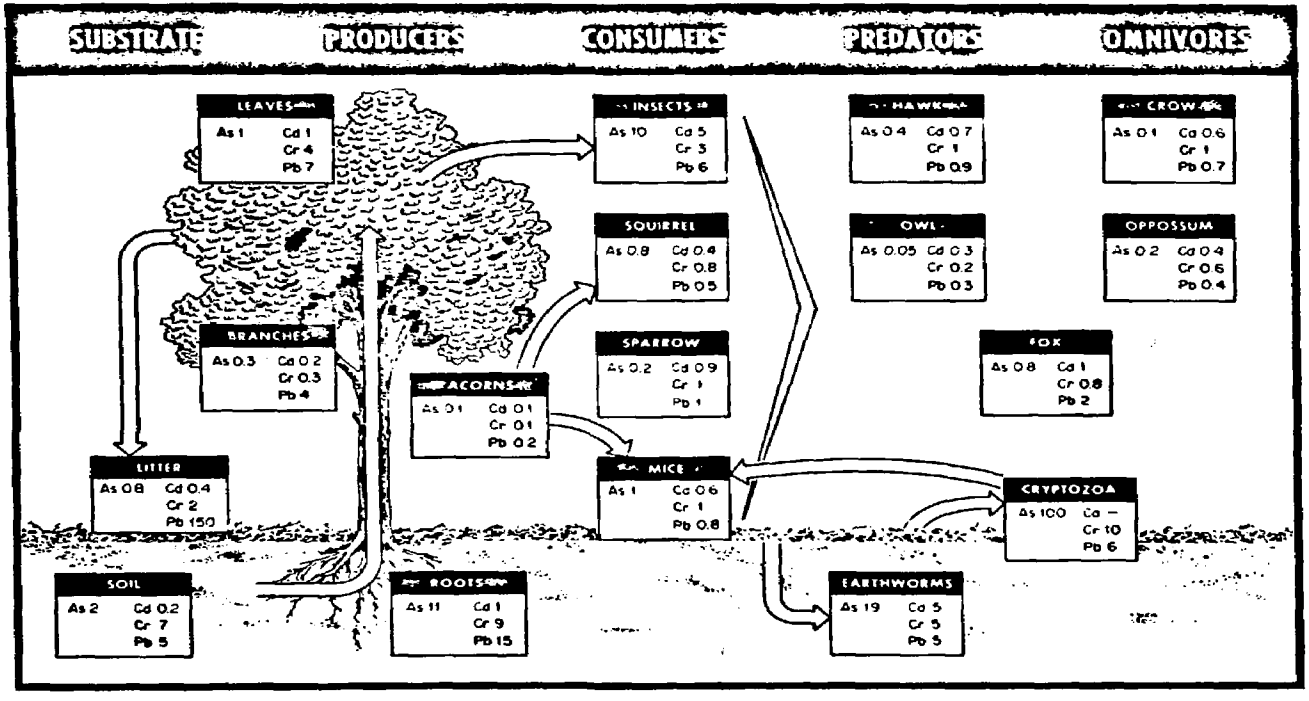


Figure 16 Elemental concentrations (ppm, dry weight) for the nonmetal (As) and three metals (Cd, Cr, Pb) in selected trophic levels of a deciduous forest ecosystem in East Tennessee.

(NRCC (1976))

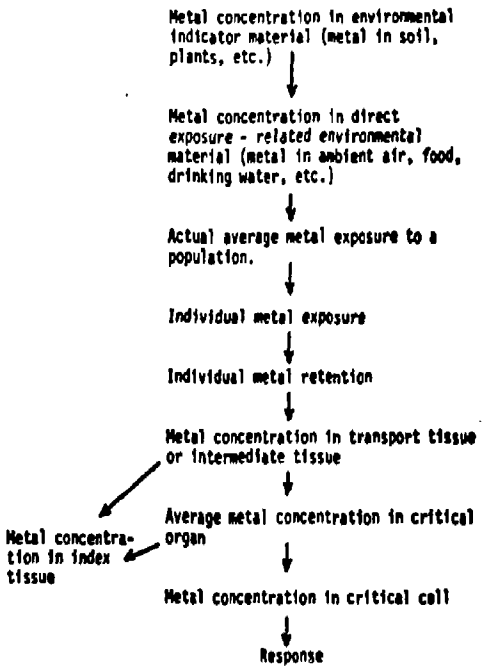


Figure 7 Sequential relationship between dose variables and a specific response (Kjellström (1976))

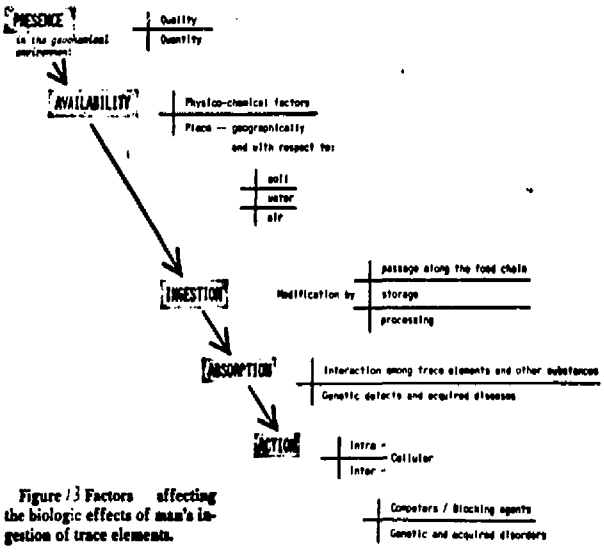


Figure 13 Factors affecting the biologic effects of man's ingestion of trace elements.

(Hopps (1975))

All trace elements above specific concentrations are toxic to humans and animals. Even those ions known to be essential for all life processes, are at higher concentrations toxic. The trace elements essential for life and growth in minute quantities are traditionally listed as cobalt, manganese, zinc, copper, iron and molybdenum. More recently flourine, vanadium, chromium and selenium have been added. For some species like rodents or chicks, arsenic, tin, silicon and nickel are now considered as essential, and well may be for humans too.

In the main the essential elements control metabolism, are part of many enzymes, and maintain the structure of proteins and nucleic acids. The elements which are considered toxic may act for example by displacing an essential element or by precipitating an enzyme, which is a protein.

Toxicity is not a simple concept. The chemical and physical nature of the agent, the concentration of the element as well as the degree of absorption by the organism may play major roles in the quantitative as well as qualitative aspects of the adverse physiological effects. Toxicity is a relative term. At very low concentrations of a needed element an organism can not live, whereas at very high concentrations this element may also prove to be lethal. These terms "low" and "high" are relative to the element. The range for zinc is quite

large, for selenium, very narrow.

There are several methods of representing the interrelationships of dose, effect and response. One of the newest methods is that of the three dimensional approach represented in Figure 19. However, it is often easier to use a two dimensional relationship such as used in Figures 20 and 21. In Figure 20 it is shown that as the dose is increased for a non-essential element (or agent), no adverse effect is experienced at first, then a reversible toxic effect can take place, followed by an irreversible toxic effect whereas, as the dose is increased for an essential element (or agent), first the deficiency of the organism for the essential element is overcome, followed by a normal range of concentrations of the element in the organism, then reversible toxic effects may take place, followed finally by irreversible toxicity. The dose-response curve for essential elements may also be expressed in a slightly different form such as that portrayed in Figure 21.

When considering the number of people exposed normally to various concentrations of a trace element, it is usually assumed that the distribution about the mean is gaussian, such as represented for lead in Figure 22. However, in actual fact we do not know whether this is an accurate representation or not. A lognormal distribution well may be more accurate.

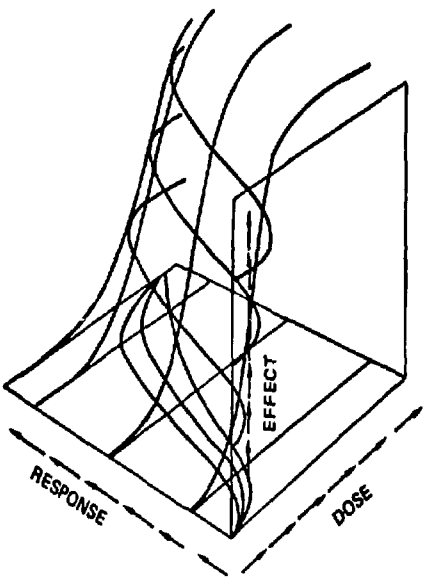


FIGURE 19 A three-dimensional representation of the interrelationships among dose, effect, and response.

(NAS (1980))

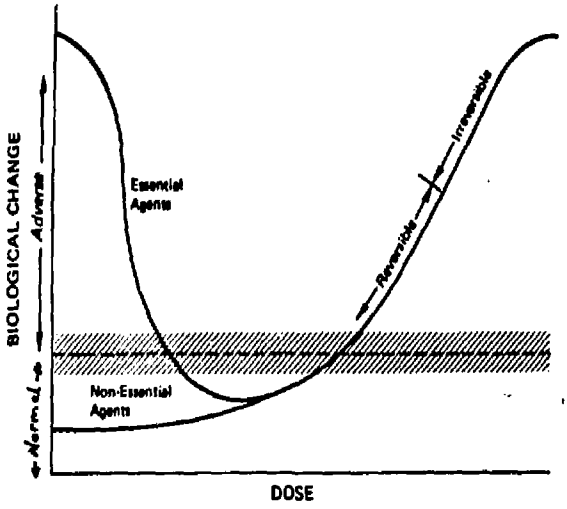
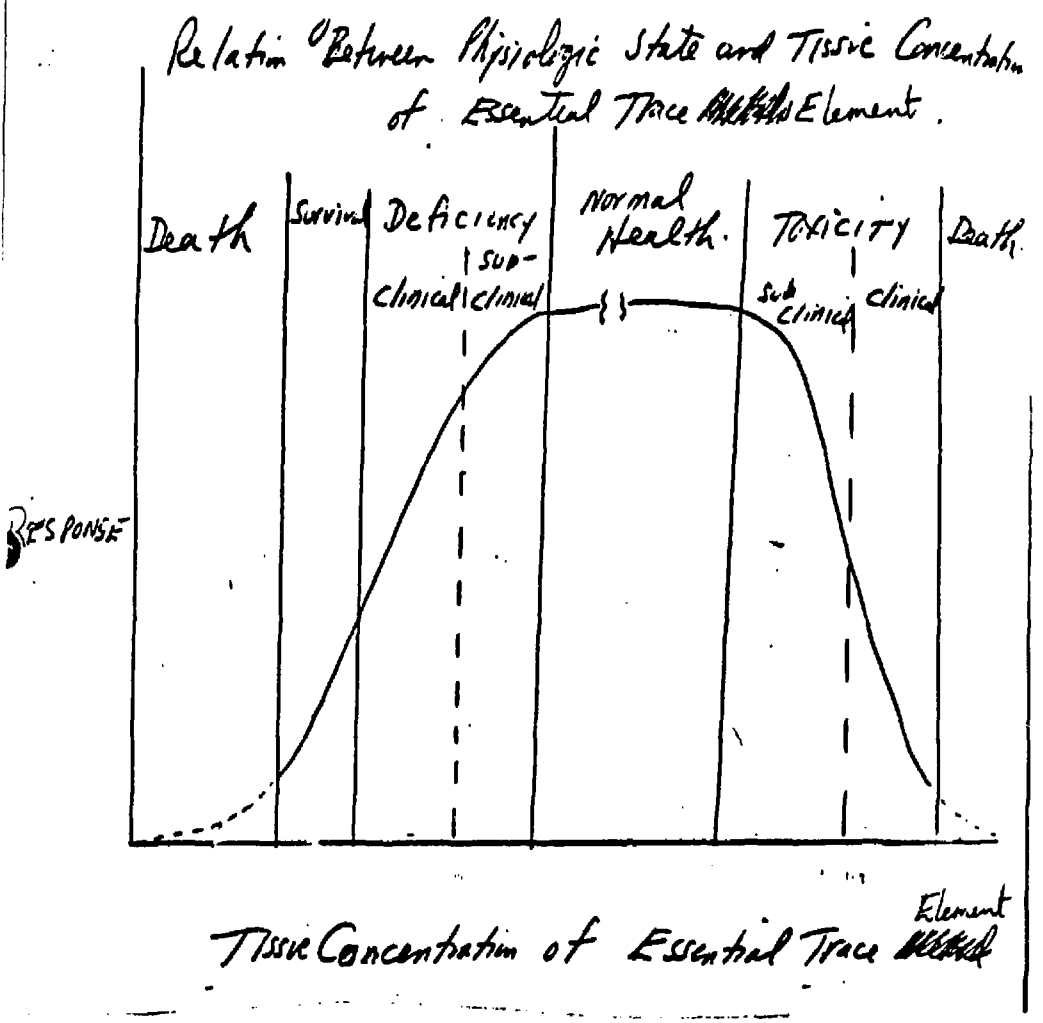


FIGURE 2.0 A generalized dose-effect relationship.

(NAS (1980))

Figure 21


Relation Between Physiologic State and Tissue Concentration of Essential Trace Element.
Death
Survival
Deficiency
sub-clinical
clinical
Normal Health.
TOXICITY
sub clinical
clinical
Death
RESPONSE
Tissue Concentration of Essential Trace Element

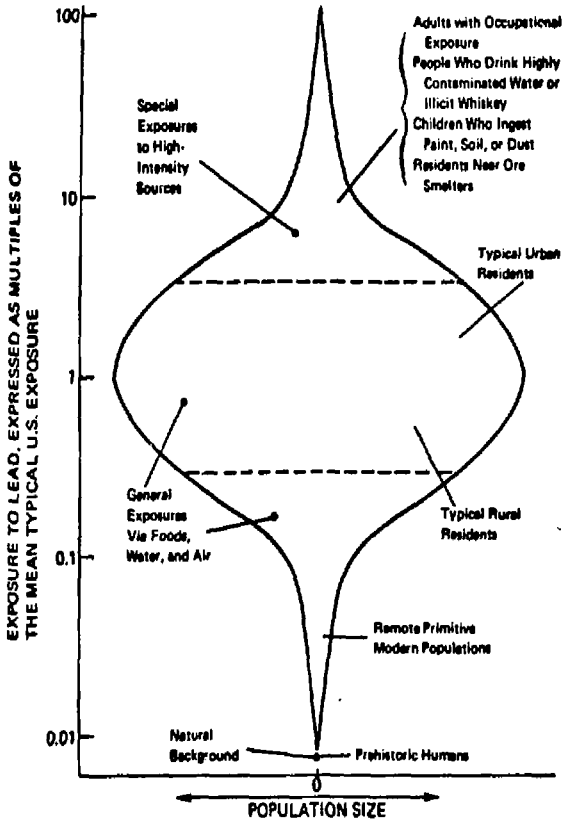


FIGURE 2.2 Schematic classification of populations according to level of exposure to lead. The actual distribution of exposures about the mean is not well documented quantitatively.

(NAS (1980))

It is often assumed that reacting dose and external exposure are equivalent. This is not always in fact true, particularly if the response is taking place at the cellular or subcellular level. The factors influencing the relationship between dose reacting (rather than a purely physical effect) at the cellular or subcellular level and the external exposure are summarized in Figure 23.

Many factors influence the toxicity of a trace element. These factors vary according to what system one is considering, for example Table 5 tabulates the factors influencing the toxicity of metals in solution, whereas Table 6 lists the factors influencing the toxicity of agents to animals and for the most part humans too.

It should be noted that Table 5 considers the presence of other metals or elements, whereas Table 6 does not. This point is often overlooked when considering animal and human toxicities. In many instances this may be due to the fact that we know little about interactions involving two trace elements, and practically nothing concerning interactions involving three or more trace elements simultaneously. One exception, however, is the triad Cu - Mo - $SO_4^{=}$, but if tungsten is considered as well (see Figure 24) our understanding becomes distinctly cloudy.

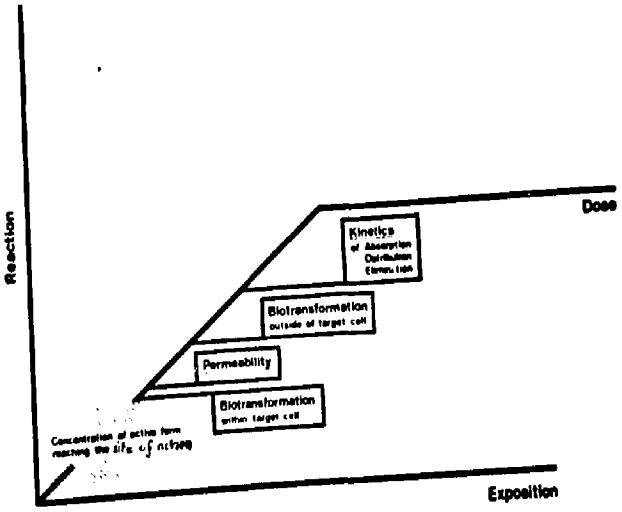


Fig. 23 Factors influencing relationship between dosage and exposure, i.e., the concentration of active form reaching the site of action

(Muller (1980))

Table 5. Factors influencing the toxicity of heavy metals in solution (Bryan, 1976)

Form of metal in water	inorganic		
	organic	soluble	ion
			complex ion
			chelate ion
			molecule
		particulate	colloidal
			precipitated
			adsorbed
Presence of other metals or poisons	joint action		more-than-additive
	no interaction		additive
	antagonism		less-than-additive
Factors influencing physiology of organisms and possibly form of metal in water	temperature		
	pH		
	dissolved oxygen		
	light		
	salinity		
Condition of organism	stage in life history (egg, larva, etc.)		
	changes in life cycle (e.g., moulting, reproduction)		
	age and size		
	sex		
	starvation		
	activity		
	additional protection (e.g., shell)		
	adaptation to metals		
Behavioral response	altered behavior		

Table 6. A CLASSIFICATION OF TOXICITY-INFLUENCING FACTORS

1. *Factors Related to the Toxic Agent*
   - Chemical composition (pH, choice of anion, etc.)
   - Physical characteristics (particle size, method of formulation, etc.)
   - Presence of impurities or contaminants
   - Stability and storage characteristics of the toxic agent
   - Solubility of the toxic agent in biologic fluids
   - Choice of the vehicle
   - Presence of excipients: adjuvants, emulsifiers, surfactants, binding agents, coating agents, coloring agents, flavoring agents, preservatives, antioxidants, and other intentional and non-intentional additives

2. *Factors Related to the Exposure Situation*
   - Dose, concentration, and volume of administration
   - Route, rate, and site of administration
   - Duration and frequency of exposure
   - Time of administration (time of day, season of the year, etc.)

3. *Inherent Factors Related to the Subject*
   - Species and strain (taxonomic classification)
   - Genetic status (littermate, siblings, multigeneration effects, etc.)
   - Immunologic status
   - Nutritional status (diet factors, state of hydration, etc.)
   - Hormonal status (pregnancy, etc.)
   - Age, sex, body weight, and maturity
   - Central nervous system status (activity, crowding, handling, presence of other species, etc.)
   - Presence of disease or specific organ pathology

4. *Environmental Factors Related to the Subject*
   - Temperature and humidity
   - Barometric pressure (hyper- and hypobaric effects)
   - Ambient atmospheric composition
   - Light and other forms of radiation
   - Housing and caging effects
   - Noise and other geographic influences
   - Social factors
   - Chemical factors

(Doull (1980))

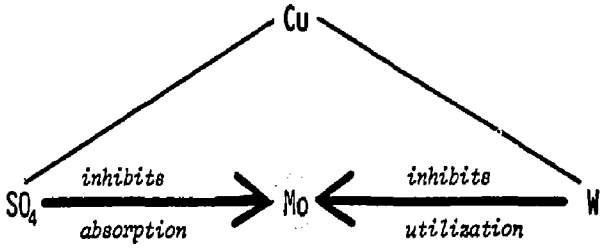


Figure 24Schematic representation of how most trace elements (for example, molybdenum) are affected by complex interactions that control their biologic effects.

(Hopps (1975))

In body cellular functions, trace elements play various roles. For example they are essential for oxygen transport, for detoxification metabolism, in one instance a metal is an integral part of a vitamin (cobalt and vitamin B_{12}), and most often as co-enzymes, which are essential for the functioning of a vast variety of enzymes. It should be noted that many elements fulfill more than one essential function in the mammalian body.

There are three categories of enzymes metal involvement: a) true metalloenzymes where a single metal is tightly bound and cannot be removed or replaced by normal chemical means, b) enzymes which require specific elements for activation, and c) enzymes which can be activated by one of many ions.

The ion may function to bind the reacting chemical (called "substrate") to the enzymes; the ion may aid the enzymes in assuming a special conformation to help bind the substrate, or the ion may be involved in the oxidation-reduction aspect of enzyme action.

Some elements other than those required by enzymes, may modify enzyme kinetics. They may, by virtue of their geometric properties, or their electronic configuration displace the essential trace element and thus partially or totally inhibit the enzyme action; pathological changes or even death to the

organism can ensue. Similarity in electronic structure of essential and toxic metals is discussed by Brakhnova (1975) who related electronic structures and properties. Two other properties of great importance when considering trace element inhibitions and interactions are ionic radius (and hydrated radii) and ionization potential (which is a measure of binding power) of the elements.

Table 7 relates the interaction of competing elements, the possible binding site in the enzymes or proteins and examples where these interactions are important.

Table 8 lists some of the known interactions between various trace elements.

There are at least five possible mechanisms to explain the toxic interaction between trace elements:

1. Displacement of an essential trace element by the heavier one in the same periodic group, e.g., zinc by cadmium, and copper by silver.
2. Displacement of an essential trace element by a similar one in a contiguous group, e.g., copper by zinc, cobalt by nickel, or iron by cobalt.
3. Displacement of an essential trace element by one with a similar ionic radius copper by

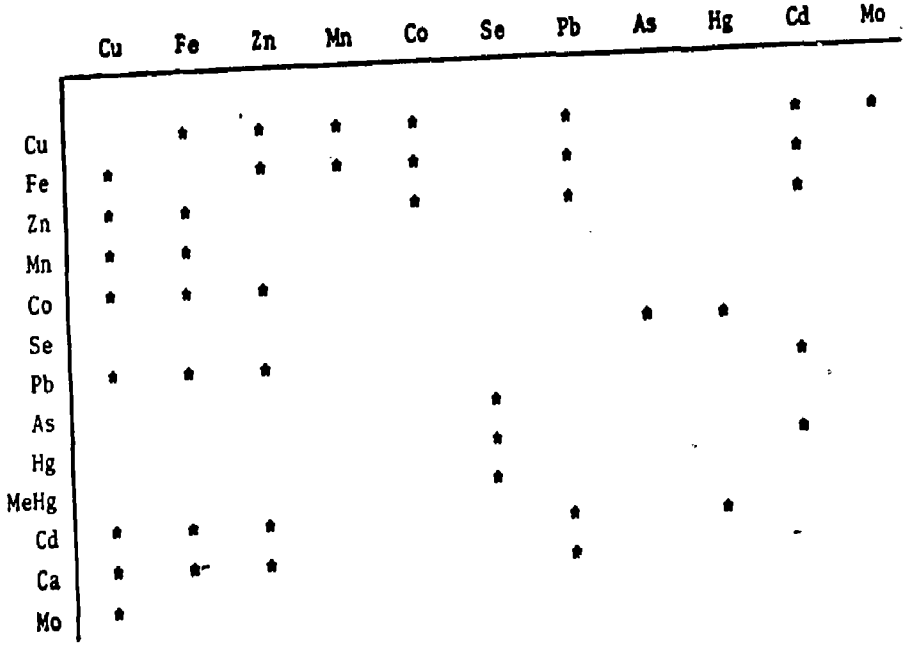
Table 7-

ELEMENTS LIKELY TO COMPETE WITH EACH OTHER ON BIOLOGICAL SITES

Element	Competing element	Preferred ligand	Probable mode of action (see text)	Example
Vanadium	Niobium, manganese	?	1	Oxidation of 5-OH tryptophane
Chromium	Zirconium, molybdenum	Insulin?	3?	Aortic plaques
Manganese	Magnesium, iron	PO_4	3?	--
Iron	Cadmium, zinc, copper, manganese	Porphyrin	2	Anemia
Cobalt	Lead, iodine	Porphyrin	4	--
Nickel	Copper	O-N	4	Tyrosinase
Copper	Molybdenum, silver, nickel, cadmium, zinc, mercury	SH	1,2	Tyrosinase
Zinc	Cadmium	SH	1	Carboxypeptidase inhibition
Molybdenum	Copper, SO_4, tungsten	Flavin	3,4,5	Tungsten inhibition of xanthine oxidase
Selenium	Sulfur, arsenic, cadmium mercury, tellurium	SH	1,5	Displacement in Keratin
Phosphorus	Arsenic	PO_4	1	Arsenolecithin
Magnesium	Beryllium	PO_4	1,4	Rickets
Calcium	Strontium	PO_4	1	Rickets

Schroeder 1973

Table 8. INTER-ACTIONS of Elements



nickel, or zinc by cobalt.

4. Displacement of an essential metal on a metalloprotein by one with a greater affinity for the protein ligands, e.g., cobalt by zinc, manganese by iron, iron by zinc, or iron by copper. The ionization potential of the trace elements is an excellent measure of the binding power of metals for protein ligands.
5. The competing element forms an extremely stable complex with the essential element, e.g., beryllium phosphate.

Humans obtain the greater portion of their trace element intake from food and water rather than from the air (unless there is a high occupational exposure). It should be noted that the percentage absorption of trace elements from food and water is often very different and the percentage absorption from assorted types of food may vary depending upon many factors, such as fiber content.

Table 9 attempts to list the normal intakes of trace elements, however this table should be revised in the light of more recent data. Table 10 estimates the proportion of total intake (not absorption) received from water sources. This table is particularly interesting, when one considers that under the consent decree water notices of the E. P. A.,

Table 9

Normal Intake, Retention and Body Content of Accessory Metals

	INTAKE per day					retained in body	total body content	organ storage with age
	food	water	air	total	%orally absorbed			
Aluminum, mg	45	+(?)	0.1	45	0.1	0.005	61	lung
Antimony, ug	<1	48	0.05	50	poor	+ve	7,900	spleen, liver, kidney
Arsenic, ug	20	2	0.02	22	80	+ve	18,000	skin, most others
Barium, ug	645	105	26	776	1-15	lung	22,000	lung, bone
Beryllium, ug	12	1	0.01	13	0.01	lung	36	lung, most others
Bismith, ug	0	20	0.01	20	8	?	200	
Boron, mg	1.1	0.23	?	1.3	99	0	48	bone
Cadmium, ug	50	3	3	56	64	3	38,000	prostate, kidney, liver
Cesium, ug	9	2	0.025	10	74-94	?	1,500	
Chromium, ug	250	5	0.3	255	10*	loss	1,400	lung
Cobalt, ug	290	10	0.1	300	73-97	0	1,500	
Copper, mg	3.5	0.06-0.5	0.02	3.7	32-60++	0	72	
Fluorine, mg	1	1.4	?	2.4	80-90	0.02	2,600	bone
Germanium, mg	1.5	?	+ve	1.5+	96	+ve	20(?)	spleen, most others
Iron	13	0.14	0.027	13	6.5	0	4,200	lung
Lead, ug	260	24	20	304	5-14**	4	121,000	bone, brain, prostate
Lithium, mg	2.0	+	?	2.0+	90	0	2.2	
Manganese, mg	3.7	0.064	0.002	3.8	3.4	0	12	

Table 7 (cont.)

	INTAKE per day				orally absorbed	retained in body	total body content	organ storage with age
	food	water	air	total				
Mercury, ug	10	0	0-50	10-60	5-10+++	+	13,000	kidney, brain
molybdenum, ug	280	16	0.1	300	40-60	0	9,300	
Nickel, ug	600	10	0-6	611	1	0	10,000	skin, lung
Niobium, ug	600	20	0	620	40-60	?	120,000	
Rubidium, mg	1.5	?	?	1.5+	90	0	320	all
Selenium, ug	150	?	?	150	60***	0	21,000	kidney
Silicon, mg	3.5	?	15	20	?	?	18,000	lung
Silver, ug	70	?	?	70	poor	+ve	800	
Strontium, mg	1.8	0.1	?	1.9	38	0	340	bone, kidney
Tellurium, ug	600	0	0	600	20-50	+ve	7,000	bone, liver, kidney
Thallium, ug	2	0	0.05	2	95	+ve	?	
THorium, ug	3	0.05	?	3	0.06-0.6	+ve	?	
Tin, mg	4.0	0	0.003	40	2	0.0055	5.8	heart, lung
Titanium, ug	850	2.1	0.7	853	1-2	lung	9,000	lung, heart
Uranium, ug	1.3	0.6	0.007	1.9	5	0.033	90	
Vanadium, mg	2.0	0.1	0.002	2.1	5	0	25	fat, lung
Zinc, mg	13	1	0.012	14	31-51	0	2,300	
Zirconium, mg	3.5	0.65	+ve	4.2	0.01	?	420	

Footnotes

+ Pulmonary absorption 25-50%; children oral absorption 50%, but retention small

Table 9 (cont.)

* Cr^{3+} salts absorption less than 1%; Cr^{6+} salts 10%; however absorption from food may be as high as 50%

** Food abso tion 45%, water 0%. Calcium reduces food F^- absorption, phosphorus enhances it.

** Food absorption 5%, water absorption 10%, children oral absorption 50% but retention 18%

*** Elemental Hg oral less than 0.01%, pulmonary 75-85%

Inorganic Hg oral 8-15%, pulmonary 10-50%

Alkyl Hg oral 95%, pulmonary 50-80%m percutaneous (guinea pigs) 6%

Phenyl Hg oral 45% absorption

*** Pulmonary absorption is higher than oral absorption (no quantitative data available), percutaneous absorption may be several percent too.

Table 10.

INCREMENT OF BULK AND TRACE ELEMENTS IN DRINKING WATER TO TOTAL DAILY INTAKES

Elements	Intake from water		Average intake from food and water (mg/day)	Proportion of total intake from water	
	Median (mg/day)	Maximum (mg/day)		Median (%)	Maximum (%)
Essential					
Calcium	52	100	800	6.5	11.8
Magnesium	12.5	40	210	5.9	16.8
Sodium	24	100	4400	0.5	2.2
Potassium	5.2	10	3500	0.09	0.3
Vanadium	<0.006	0.02	2	0.6	1.0
Chromium	0.001	0.01	0.1	1.0	9.2
Manganese	0.01	0.2	3	0.3	6.3
Iron	0.09	0.3	15	0.6	2.0
Cobalt	0.006	0.01	0.3	2.0	3.3
Nickel	0.005	0.02	0.4	1.3	4.8
Copper	0.02	0.2	2.5	0.8	7.5
Zinc	0.5	2.1	13	3.8	14.4
Selenium	<0.02	–	0.15	<13.3	–
Fluorine	0.4	1.0	1.8	22.2	41.7
Molybdenum	0.003	0.02	0.34	0.9	5.6
Nonessential					
Silicon	14.2	60	>20	<71.0	<90.0
Aluminum	0.1	1.0	45	0.2	2.2
Barium	0.09	0.76	1.24	7.3	59.8
Strontium	0.22	1.0	2	11.0	40.0
Boron	0.06	0.2	1.0	6.0	17.5
Bismuth	Trace	–	0.002	–	–
Beryllium	Trace	–	0.00001	–	–
Antimony	Trace	–	<1.0	–	–
Lead	0.007	0.02	0.41	1.7	4.7
Lithium	0.004	0.1	2.0	0.2	4.7
Silver	0.0005	0.001	0.07	0.7	1.4
Tin	0.002	0.005	4.0	0.05	0.1
Titanium	<0.003	0.01	0.3	0.1	3.2
Uranium	0.0003	0.004	1.4	0.02	0.3
Cadmium	0.005	0.04	0.07	7.1	58.1

(Schroeder (1973))

oral intake of trace pollutants is considered to be water plus 6.8 gm. of fish only. Let us consider the cases of arsenic, asbestos, cadmium, chromium, lead and nickel in more detail.

A R S E N I C

The human biocycling of arsenic needs a great deal of clarification. One of the main reasons is because the accuracy of concentration measurements leaves much to be desired and may in many instances be off by a factor of 10. In addition, we know little concerning the natural ratios of the various species of arsenic, and further the amount of arsenical flux per year in the U. S. has dropped precipitously, since arsenic is no longer a component of commonly used pesticides.

As a general rule the toxicity of arsenical compounds decreases as follows: arsine (-3) > organo-arsine derivatives > arsenites (+3) > arsenoxides (+3) > arsenates (+5) > penta valent organic compounds (+5) > arsonium metals (+1) > metallic arsenic (0). Thus in most instances inorganic arsenicals are more toxic than organic ones and the trivalent states is more toxic than the penta valent state. It should be noted that trivalent arsenic is converted via the methyl and dimethyl forms to penta valent arsenic both in vivo and in vitro. The reverse has been shown in vitro and <u>may</u> also be true in vivo.

When arsenic is absorbed via the lungs or via the gastro-intestinal system about 90% is excreted rapidly via the urine, with a biological half-life of under 2 days. Only a couple of percentage are excreted via the feces. It is of great importance to note that the rat and probably also the cat, excrete arsenic very slowly unlike humans, hence it is wise to be doubly critical of applying data obtained from the use of these species to humans. In the past this has not been done and has helped to confuse the general metabolic picture when applied to humans.

At present, the figures obtained for the human environmentally produced consumption of arsenic differ by an order of magnitude from those obtained overseas. This question needs resolution, since much of the work showing detrimental effects, due to arsenic, involves overseas populations, and often more than one trace element may be suspect.

At the present time, the following is a best estimate of the "normal" amounts of arsenic absorbed by a non-occupationally exposed person: -

Inhalation - assuming a daily ventilation rate of 20 m^3/day, 30% absorption and an ambient arsenic level of 0.003 $\mu g/m^3$, the amount absorbed would be 0.02 μg. For cigarette smokers smoking a pack of cigarettes per day the amount absorbed would be 2 μg. Ingestion of potable water, at the rate of 2 1/day which contains 1 ug arsenic/1 would lead to an absorption of just under

2 μg, since about 95% is absorbed. The F. D. A. considers that the present day U. S. food contains about 21 μg of arsenic per day and if an average absorption of 75% is assumed (the absorption from meats, poultry and fish seems higher and that from vegetables and fruits probably is lower), the amount absorbed from food would be about 16 μg. Therefore a non-smoker would absorb about 19 μg/day and a smoker 21 μg/day. At present the overseas absorption amounts seem to be about an order of magnitude higher.

So far arsenic deficiencies have been shown in rats, chickens, goats and mini-pigs at about the 50 μg/gm of food level. Thus it would probably be difficult to find a naturally occurring arsenic deficient population amongst humans, but it is also difficult to theorize that arsenic is a carcinogen at low levels. It should also be noted that supplemental arsenic in feeds of pigs and poultry promotes growth.

Figure 25 illustrates some of the sources, both natural and man induced, which can lead to increased arsenical exposure to man. A survey of dose levels versus chronic effects produced in man, has led one of the authors (I. H-B) to seriously question whether arsenic acts on its own or whether like molybdenum, one of its more usual methods of action requires the presence and activity of one or more additional ions.

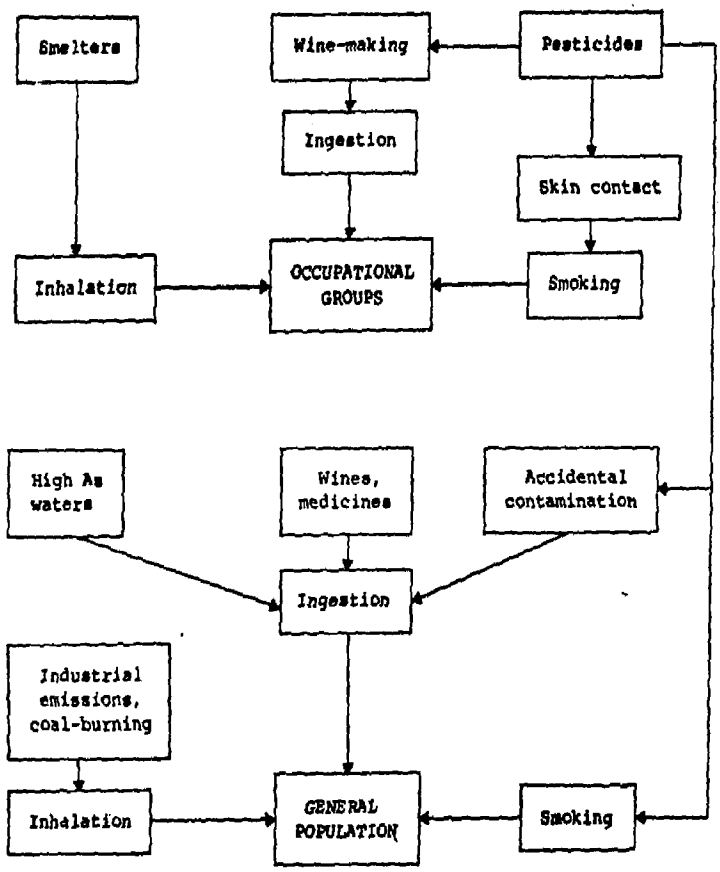


Fig. 15 Arsenic : sources and pathways to humans

(Waller (1979))

A S B E S T O S

Asbestos - as it occurs naturally - is a rock, as solid and dense as granite. It is found underground in thin veins or layers between greater thicknesses of rock that are chemically very similar.

The name 'asbestos' may be given to any naturally occurring mineral that can be handled or processed into fibres. There are thirty or more distinct types forming what is known as the Asbestiform group, but only six have any commercial significance. These are, in order of importance, Chrysotile or White asbestos, Crocidolite or Blue asbestos, Amosite, Anthrophyllite, Tremolite, and Actinolite. These fall into two main groups: Chrysotile (or Serpentine) asbestos and Amphibole asbestos. The differences between the various types result from the rock or matrix in which asbestos occurs. Chemically all are complicated magnesium silicates usually containing one or more of the following metals: sodium, aluminum, iron and calcium, as well as trace elements such as cobalt, nickel and chromium.

White asbestos or Chrysotile is by far the most important variety of asbestos, accounting for 80 to 90 per cent of the world's output. It is found chiefly in Canada, Russia, and Zimbabwe. Its color varies from a pure white to greyish-green depending on the impurities present.

Some Chrysotile fibers are up to three inches long, though most are under one and a half inches long. They are strong and flexible and easy to work, probably because of amounts of talc which are found with them.

When the asbestos rock is milled, it breaks down into fibers and the adjacent rock powders and so the two are readily separated. Very fine fibers can be obtained by rubbing the rock surface; these are, in fact, bundles of fibers which can be subdivided. By using the electron microscope the diameters of the finest fibers have been measured at between one millionth and one ten-millionth of an inch. In practice the fibers used are very much thicker than this. Recent studies with the electron microscope suggest that Chrysotile fibers are hollow, though the tubes may be filled with less crystalline material having the same chemical composition. This would account for the fact that the fibers are soft, elastic and absorbent.

Amphibole asbestos -- The types of asbestos in this group differ from Chrysotile in containing more silica, iron, aluminum, sodium, and calcium but less magnesium. Each contains two or more of these metals in varying proportions Crocidolite (this has a distinctive blue color) and Amosite (this varies in color from white to yellowish brown) are the most important varieties of Amphibole. Both are iron silicates, the former

containing two kinds of iron and sodium, and the latter containing ferrous iron and magnesium.

Crocidolite occurs mainly in South Africa, but there are also large deposits in Bolivia and Australia. Amosite is found only in South Africa.

Amosite may have fibers up to a foot long, hence it is less flexible and its fiber strength is less than Chrysotile and Crocidolite. Amphibole fibers are not only longer than those of Chrysotile but they are also larger in diameter (one two hundred and fifty thousandth of an inch versus one millionth of an inch). They are also solid and thus are hard and springy but brittle.

Crocidolite fibers are those most likely to produce mesothelioma.

The urban atmosphere can contain 10-100 ng/m^3 but values up to 500 ng/m^3 have been detected near factories processing asbestos.

Average drinking water ranges from 0.3-1.5 mg/l in the eastern U. S. whereas Canadian values have been measured at 2-175 x 10^6 fibers/l. Asbestos fibers have been found in some alcoholic beverages probably due to the use of asbestos filters.

C A D M I U M

In the last 5-10 years a tremendous amount of research has been published concerning the exposure and health effects due to cadmium.

As an average, in the urban dweller typical daily intakes and amounts absorbed are as follows: -

1) Air exposure: 0.1 µg Cd/day (assuming a daily inhalation of 20 m^3 and 25% deposition) and amount absorbed from the air 0.06 µg Cd/day (assuming 64% absorption)
2) Food intake: 43 µg Cd/day and amount absorbed from food 2.6 µg Cd/day (assuming 6% absorption)
3) Water intake: 3 µg Cd/day and amount absorbed 0.2 (assuming 6% absorption)
4) A smoker smoking 40 cigarettes/day would absorb a further 1.9 µg Cd/day.

   Thus an average urban non-smoker would absorb about 2.9 µg Cd/day, whereas an urban smoker would absorb about 4.8 µg Cd/day.

It has been known for about 25 years that the organ most likely to suffer damage from "overexposure" to cadmium is the kidney. Thus the kidney is called a "critical" organ for cadmium exposure. It has also been found that as the human ages up to about 50 years of age the content of cadmium in the kidney increases, after that age the average content levels

off. It has been estimated (CEC 1978) that if 10-20 µg Cd was absorbed via the gastrointestinal tract for 70 years threshold level kidney damage might result. Therefore the exposure of an urban smoker would have to be doubled before kidney damage might probably result.

Figure 26 illustrated the various sources by which the exposure of the general population, may be increased. The figure also lists some of the occupations leading to increased cadmium exposure.

C H R O M I U M

Chrome ore is always found in conjunction with other metals (for example ferrochrome) as an oxide. The two largest deposits are in South Africa and the Soviet Union. Zimbabwe long considered a large and important source has declined in importance due to the deposits being worked out. The two main forms of chromium are Cr(+3) and Cr(+6).

Industrial production and handling of certain Cr(+6) products have been associated with allergic Cr dermatitis and slow healing skin ulcerations. Land dumping of industrial wastes have been responsible for groundwater contamination in a number of instances.

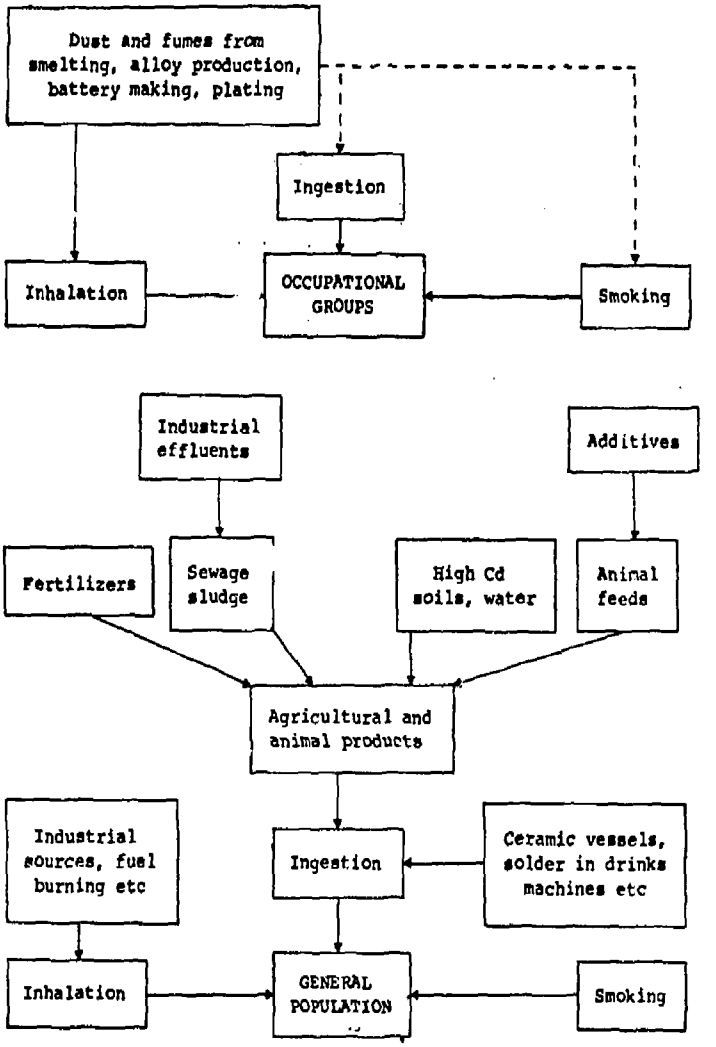


Fig.26 Cadmium : sources and pathways to humans

(Waller (1979))

Background levels of Cr in air average 1 ng/m^3 in rural settings and 10-60 ng/m^3 in urban environments. Uncontaminated water concentrations average 1 ppb, whereas municipal drinking water contains up to about 35 ppb. Most of the Cr(+3) present in water is absorbed onto particulate matter, whereas Cr(+6) remains in solution. The Cr(+6) is reduced to Cr(+3) when it reacts with animal or vegetable material in the water. Most foodstuffs contain about 0.2 ppm Cr on the wet weight basis for an average daily human food intake of 250 μg/day.

Cr(+3) is the commonest naturally occurring form of chromium (for example chromite) and is the form which functions biologically as an essential element in mammals where it maintains efficient glucose, lipid and protein metabolism. The toxicity of Cr(+3) is low because of poor membrane permeability.

Studies from Jordan, Nigeria and Turkey have provided evidence that chromium (+3) deficiency is one etiological factor in the impaired glucose tolerance in protein - calorie malnutrition. In addition correction of certain types of impaired glucose tolerance in some middle aged and elderly subjects in the U. S. has been achieved by dietary supplementation with chromium. Poor chromium nutrition (high sugar consumption may deplete chromium stores by enhancing urinary

excretion) has been suggested as an etiological factor in coronary heart disease. No accurate figures are available to assess at what levels chromium is deficient. The concentration (or stage at which it becomes toxic will depend partially upon valence state).

L E A D

The intakes and absorption of lead by humans has been very well studied, although we still have a lot to learn, particularly with respect, to being able to reduce absorption or increase excretion without resorting to therapeutic complexing agents.

Figure 27 illustrates graphically the quantitative differences in the amount of lead absorbed by urban smokers versus rural non-smokers, whereas Table 11 tabulates exposures and amounts absorbed in a slightly different form. Since under "normal" conditions the largest exposure for humans comes from foods, it is of interest to determine how much the lead content of foods increases in contaminated areas. Some typical results are tabulated in Table 12.

Figure 28 illustrates a simple 3 compartmental model for absorption, retention and elimination of lead in adult human males. The blood lead levels reflect fairly well the lead status of the human body, to a first approximation,

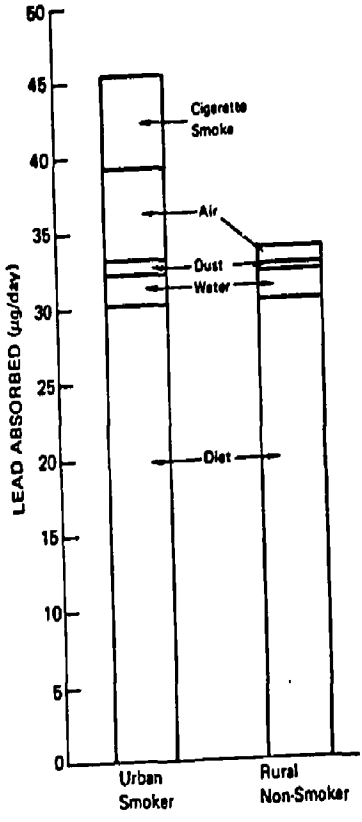


FIGURE 27 Estimated contributions of different sources of exposure to the total lead absorbed by two different subsets of the general population.

(NAS (1980))

TABLE II. Estimated Exposures to and Absorption of Lead for a Typical Adult under Arbitrarily Defined Natural Conditions

Route of Exposure	Concentration of Lead in Environment	Amount Inhaled or Ingested Per Day	Absorption Factor	Amount of Lead Absorbed (μg/day)	Percent of Total Lead Absorbed
Air	0.0001 μg/m³	20 m³	0.4	0.0008	0.03
Water	1 μg/l	2 l	0.1	0.2	8.5
Diet	0.01 μg/g	2,000 g	0.1	2.0	85.1
Soil	15 μg/g	0.1 g	0.1	0.15	6.4
TOTAL				2.35	100.0

(NAS (1980))

Table 12. Concentration of lead in (or on) plants and food products.

Specimen and description	Lead (ppm)		
	Contaminated area		Uncontaminated area
	Minimum	Maximum	Maximum
Potato			
Whole	1.10	13.10	1.10
Peeled	0.37	2.50	0.10
Green salad			
Unwashed	3.54	185.0	1.0
Washed	2.18	71.2	0.50
Cabbage			
Unwashed	1.18	7.44	0.23
Bean			
Within pod	-	25.90	1.0
Pod removed	0.41	1.37	0.05
Bread			
From farmer	0.89	10.5	0.46
Bacon			
From farmer	0.34	2.04	0.25
Honey			
From farmer	0.89	7.80	0.46
Milk			
From farmer	1.6	1.9	0.02
Hay			
From farmer	120.0	430.0	10.0

(NRCC (197))

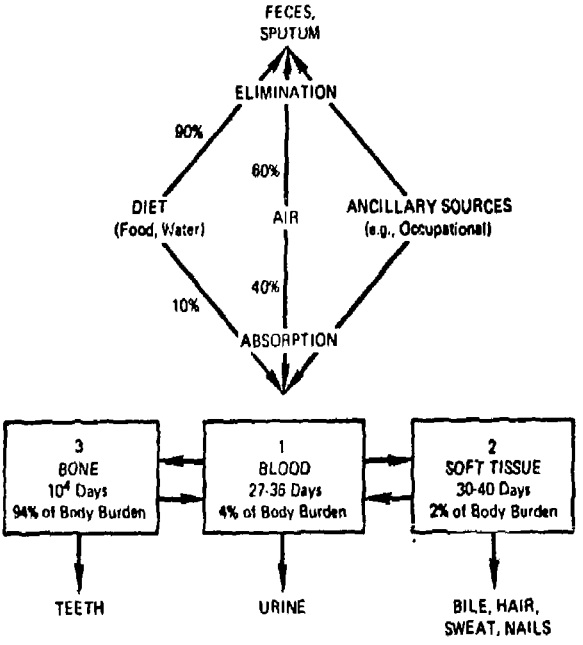


FIGURE 28 A simple three-compartment model for absorption, retention, and elimination of lead in humans. Quantitative estimates apply to adult males.

(NAS (1980))

what biological changes may be taking place - see Table 13.

N I C K E L

Although nickel was mined in New Caledonia before the Canadian Sudbury complex was discovered, it was eclipsed by Sudbury because of the latter's higher quality. Copper, platinum and cobalt are also mined at Sudbury.

Nickel activates a number of enzymes in vitro, for example arginase. It also appears to have a role in maintaining the structure of nucleic acids and membranes and in lipid metabolism. Nickel is poorly absorbed and is mainly excreted in the feces. Extrapolation from animal data, suggests that the dietary requirement for adults is about 50-80 ng/g diet, which is equivalent to about 30 µg/day (Casey and Hambridge 1980). There appears to be an interaction between nickel and iron when nickel is deficient. The elucidation of the nickel-iron interaction may well provide an insight into the physiological role of nickel.

Nickel like Chromium is a contact-sensitizer and allergen. Nickel interacts with Co, Cu, Fe and Zn which is not surprising when it is considered that they all have similar ionization potential (which is a measure of binding capacity to organic ligands, including amino acids).

TABLE 13 Summary of Lowest Blood Lead Levels Associated with Specific Biological Changes in Children

Blood Lead Level (μg Pb/100 ml)	Effect
10	ALAD inhibition
15-20	Erythrocyte protoporphyrin elevation
40	Increased urinary ALA excretion
40	Anemia (lowered hemoglobin count)
40	Coproporphyrin elevation
50-60	Cognitive (CNS) deficits
50-60	Peripheral neuropathies
80-100	Encephalopathic symptoms

(NAS (1980))

Trace elements may adversely affect many organs and systems, if the concentrations to which persons are exposed, are high enough. Beliles (1975) summarized some of the results found during occupational and/or accidental poisoning and the findings are tabulated in Table 14.

When one thinks of trace elements "causing" diseases it is often thought in regulatory circles only in terms of carcinogenesis and more recently teratogenesis. This is not accurate, since we know trace elements are involved in many types of disease processes, probably the best known example being, copper and Wilson's disease. A group of diseases which have also received much attention with regard to trace element involvement are cardiovascular group. Tables 15 and 16 summarize some of the suspected trace element involvements, but in each instance further confirmatory evidence is required.

When considering mutagenesis, carcinogenesis and teratogenesis it should always be remembered that they are <u>not</u> equivalent, that is, if a substance is a mutagen it need not be a teratogen and vice versa and if a substance is a teratogen it need not be a carcinogen and vice versa. However, there is a good deal of overlap and many substances belong to two or even three of the categories, mutagen, carcinogen and teratogen.

TABLE 14

	Industrial Hazard		F.E.N.D.	Target Organs										Carcinogenic	Teratogenic
				GI	RT	CNS	CVS	L	SK	B	K	BN	END		
Aluminum		+	+		+										
Antimony	AP	++		+	+		+	+	+						
Arsenic	AP	++		+	+	+		+	+	+			+	humans	animals
Barium		+		+	+	+	+		+						
Beryllium		++	+		+				+			+		animals	
Bismuth		+						+	+		+				
Boranes		+			+			+			+				
Boron				+		+									
Cadmium	AP	++	+	+	+	+	+				+	+		animals/humans	animals/humans
Chromium		(VI)+			+	+		+	+		+			(VI) animals/humans	concentrates in fetus
Cobalt		+		+	+	+	+		+				+	animals	
Copper	AP	+		+						+					
Gallium		+				+			+		+	+			
Germanium		+		+	+		+								
Gold		+						+	+	+	+				
Hafnium		+						+	+						
Indium		+				+		+			+				animals
Iron	AP	+	+	+	+	+		+		+			+	animals(humans)	concentrates in fetus
Lanthanons		+			+			+		+					
Lead	AP	++	+	+		+				+	+			animals/humans	animals/humans sterility
Lithium				+		+	+				+		+		animals
Magnesium		+				+									
Manganese		++			+	+								animals	animals embryocidal
Mercury	AP	++	+		+	+					+				animals/humans conc.in fetus
Metal hydrides		++								+					
Molybdenum		+						+		+	+	+			animals embryocidal
Nickel		++	+		+	+			+					animals/humans	animals; placental transfer
Niobium		+						+			+				
Osmium					+										
Palladium		+								+					

Table 14 (cont).

	Industrial Hazard	F.E.N.D.	Target Organs										Carcinogenic	Teratogenic
			GI	RT	CNS	CVS	L	SK	B	K	BN	END		
Platinum		++		+		+		+						
Rhodium		+			+								animals(?)	
Rubidium		+			+	+								
Ruthenium				+										
Selenium		++	+	+	+		+	+					animals(?)	animals/humans
Silver		++		+				+		+				
Strontium		+				+								
Tantalum		+		+										
Tellurium		+			+		+			+				animals
Thallium	AP	++	+	+	+		+			+		+		passes through placenta
Tin (organic)	AP	++	+		+									
Titanium		+		+									animals	animals
Tungsten		?			+									
Uranium		++								+				
Vanadium		++	?		+	+			+	+			animals(?)	
Yttrium		+		+			+		+				animals(?)	
Zinc	AP(?)	+	+						+		+		animals(?)	animals
Zirconium		+						+	+					

Industrial Hazard

AP	accidental poisoning
+	limited industrial hazard
++	moderate to severe industrial hazard
F.E.N.D.	factor in environmental occupational diseases

Target Organs

GI	Gastrointestinal tract
RT	Respiratory tract
CNS	Central nervous system
CVS	Cardio-vascular system
L	Liver
SK	Skin
B	Blood
K	Kidney
BN	Bone
END	Endocrine

(Beliles (1975))

Table 15

TRACE ELEMENTS CONSIDERED INVOLVED EXPERIMENTALLY IN CARDIOVASCULAR DISEASES

Disease	Protective	Inductive
Atherosclerosis	Chromium, manganese, vanadium, cobalt	Cobalt (injected), copper, chromium deficiency
Hypertension	Zinc	Cadmium, zinc deficiency
Aortic calcification	Fluorine, magnesium	Fluorine deficiency
Elasticity of arteries	Lithium, copper	
Focal myocardial necrosis	Selenium	Arsenic

(Schroeder (1973))

Table 16

SECONDARY CHANGES IN TRACE ELEMENTS IN ATHEROSCLEROSIS AND MYOCARDIAL INFARCTION

	Increase	Decrease
Atherosclerosis		
Aorta	Iron, molybdenum, cobalt, lead, nickel, zinc	Copper, lithium, manganese, chromium
Heart	Cobalt, copper, zinc	Manganese
Plasma, or blood	Manganese	Zinc
Myocardial infarction		
Injured tissue, heart	Barium, bromine, antimony	Manganese, molybdenum, aluminum, rubidium cobalt, cesium, zinc
Serum	Copper, nickel, manganese, boron, molybdenum, calcium	Zinc, iron
Urine	Copper	

(Schroeder (1973))

Mutations, in higher organisms, can be divided into two categories (a) microlesions at the molecular level, also called point mutations, which may consist of base-pair substitutions or frameshift changes and (b) macrolesions at the chromosomal level, consisting of structural changes in the chromosomes or numerical changes in the genome see Table 17. In lower organisms, such as bacteria, mutations can only occur at the molecular level, as base-pair substitution or frameshift changes in the nucleotide sequence of DNA.

It should be noted that cells have mechanisms that tend to remove carcinogens bound to DNA and to repair the lesions introduced. Three different repair processes have been identified in mammalian cells: (a) photoreactivation repair repairing uv damage (b) excision repair occurring throughout the cell cycle and (c) post replication repair confined to the period of DNA replication. The first evidence of the importance of DNA repair mechanisms was derived from fibroblast cultures obtained from Xeroderma pigmentosum patients. These patients are sensitive to uv light, which induce skin tumors. DNA repair activity in the patient's fibroblasts is very low and thus their DNA is vulnerable to damage. Setlow (1978) later helped accumulate direct evidence revealing that DNA repair mechanisms are able to remove chemical carcinogens from DNA and repair the strand.

TABLE 17

TYPES OF MUTATIONAL EVENTS

Unit	Mutational change	Nature of event
Sub-chromosomal	I. Intra-locus	deletion, duplication — *frame shift* substitution — transition, transversion
	II. Inter-locus*	intra-chrom. (deletion; transposition — *transposition*, duplication, inversion) inter-chrom. (translocation)
Chromosomal	III. Aneuploidy*	monosomy, trisomy, etc.

* All class III and some class II events may be detected cytologically.

(Evans (1980))

Table 18 summarizes most of the mutagenic data available on trace elements, however care must be taken in the interpretation of the meaning of these tests since summaries often omit data which later proves of importance.

In many instances carcinogenicity is "proven" in animal models and then these results are extrapolated to human. Table 19 lists the procedural criteria and predictive factors applicable to animal models in assessment of carcinogenici and significance of extrapolation to man, whereas Table 20 documents the limiting factors in relating dose-response data in animals in assessment of carcinogenicity and probable significance to risk assessment in man. And finally in Tables 21 and 22 are listed the possible genesis of false negatives and positives in in vitro predictions of carcinogenicity in man.

A number of metals and their compounds have been shown to be carcinogenic in experimental animals. Comprehensive reviews on this subject have been published by Sunderman (1977), Furst (1977), Furst (1978) and Furst and Radding (1980).

After consideration of experimental design of the animal experiments, it was concluded that in rodents the following metals (or at least one of their compounds) were carcinogenically active:

Ni, Cr, Cd, Be, Pb, Mn.

Table 18

Resume of Experimental Observations that Pertain to Mechanisms of Metal Carcinogenesis

Experimental System	Metals whose compounds have yielded positive experimental results in the system									
	Metals that are recognized as carcinogens in humans and/or animals									Other metals
	As	Be	Cd	Co	Cr	Mn	Ni	Pb	Zn	
Aberrations in base-pairing or conformation of nucleic acids in vitro			×	×		×	×		×	Ca, Cu, Mg
Infidelity of DNA replication by DNA polymerase in vitro		×	×	×	×	×	×	×		Ag, Cu
Stimulation of RNA chain initiation despite diminution of overall RNA synthesis			×	×		×		×		Cu
Mutagenicity in *E. coli*	×		×		×					Hg, Mo, Se, Tc, V
"*Rec*-assay" in *B. subtillis*	×		×		×	×				Hg, Mo
Mutagenicity in *S. typhimurium*					×				×	Fe, Pt, Rh, Ru, Se
Chromosomal aberrations in tissue culture cells	×		×		×		×			Sb, Te
Aberrant DNA synthesis or repair in tissue culture cells	×				×		×			
In vitro transformation of tissue culture cells	×	×	×		×		×	×		
Enhanced susceptibility to viral transformation or chromosomal damage in vitro	×	×	×		×		×	×		
In vivo binding to nuclear macromolecules or organelles		×	×	×			×			
In vivo inhibition of DNA or RNA synthesis		×					×			

TABLE /9

Procedural Criteria and Predictive Factors Applicable to Animal Models in Assessment of Carcinogenicity and Significance of Extrapolation to Man

1. *Unequivocal statistical approaches and results*
2. *Reproducibility and confirmation in various species and strains*
3. *Confirmation in pathological diagnoses*
4. *Tumor incidence increase on dose-response relationship*
5. *Comparability in experimental dose to human exposure*
6. *Significance of time-to-tumor data*
7. *Narrow range in spontaneous tumor incidence (control animal population)--reproducibility of data*
8. *Protocols consistent with established principles of toxicity*
9. *Recognition of biochemical, pharmacokinetic, and metabolic mechanisms in interpretation of findings*

(Kraybill (1979))

TABLE 20

Limiting Factors in Relating Dose-Response Data in Animals in Assessment of Carcinogenicity and Probable Significance to Man (Risk Assessment)

1. *Inappropriate routes of administration*
2. *Improper test species and strains*
3. *Role of diet, nutrition, and diet contaminants*
4. *Contaminants in test agents (chemicals)*
5. *Body retention--role of lipophilic chemicals*
6. *Metabolic overload*
7. *Influence of dose on metabolic pathways*
8. *Validity of statistical procedures*
9. *Value of research probes--perspectives on dose administration and response*
10. *Humoral and hormonal factors*
11. *Prevalence of repair mechanisms*

(Kraybill (1979))

The following elements have also been studied, but for various reasons the results could be considered to be inconclusive:

Zn, Co, Fe, Al, Cu, Hg, Ti, Au, Pd, Ag, Pt and As.

The first report drew the attention to the problem of foreign body carcinogenesis. Amost any sheet, foil, or disc placed under the skin of a rat will produce fibrosarcoma at the site. Silver is in that category (Oppenheimer 1956). It is difficult to interpret the intraperitoneal injection of mercury liquid which also resulted in a fibrosarcoma (Druckrey 1957). Brand (1976) has reviewed this field.

The following elements have been associated, at least by some authors, with tumors in humans:

Ni, Cr, Cd, As, Be

One of the questions which keeps reoccurring in the mind of one of the present authors (I. H-B) is whether the first four elements listed, can function as complete carcinogens or whether initiators and/or co-carcinogens or promoters are required for these elements to act as carcinogens in humans. In reviewing the literature it soon becomes apparent that other elements and ions, which may vitally affect the immediate trace element surroundings of the human population

Table 21 Possible genesis of false-negative in vitro predictions

Negative in vitro test results for an animal carcinogen may occur for one or more of the following reasons:

1. The carcinogenic effect observed may have been mediated via a mechanism that did not involve covalent interaction of the chemical with the DNA of the host animal. For example,
   a) Hormonal carcinogens (diethylstilboestrol?)
   b) Physical carcinogens (asbestos?)
   c) Inorganic carcinogens (some nickel compounds?)
   d) Epigenetic carcinogens (includes a-c, see ref. 3; saccharin?)
2. The in vitro test system, in particular the S-9 mix, has not been *optimized* for the particular class of compound under study. The use of *structurally appropriate positive* control chemicals alerts to this situation
3. An *inappropriate* in vitro assay is being employed for a particular class of compounds

Table 22 Possible genesis of false-positive in vitro predictions

Positive in vitro test results for a putative non-carcinogen may occur for one or more of the following reasons:

1. The chemicals' non-carcinogenic status has been defined inadequately. For example,
   a) Too short a study period or too low a dose level employed.
   b) "Inappropriate" route of administration used.
   c) "Inappropriate" test-animal species used.
   d) Inadequate pathology undertaken.
2. The in vitro test has failed to take account fully of the deactivation processes that operate on active electrophiles in vivo (either enzymic or chemical).
3. Whole body chemical transport effects, which may influence access of the chemical to DNA in vivo, are not adequately represented in the in vitro assay.
4. The in vitro assay is responding positively to a physical or chemical (or physicochemical) property of the chemical which is not cancer-related.

(Ashby (1980))

at risk, are present either in deficien or excess amounts. Often two or three articles on a particular population must be reviewed before at least a partial picture is uncovered.

Thus it becomes important to attempt to postulate a possible mechanism of carcinogenesis for Ni, Cr, Cd, As and Be. It also is necessary that the mechanisms be able to explain negative results (both human and animal). It should be noted that there is no animal model for arsenic. Further, since Ni, Cr(+3), As and possibly Cd are essential elements, one needs to know at what concentrations and/or under what circumstances they cease to be essential and become a carcinogenic risk to the human body.

In 1969 Furst and Haro postulated that carcinogenic metals would interact with DNA, possibly causing damage via say in some instances an irreversible chelate.

Sunderman (1979) in an attempt to suggest mechanisms looked at six parameters: -

I. Interaction of metals with nucleic acids

II. Impairment by metals on the fidelity of DNA replication by DNA replication polymerase in vitro

III. Mutagenicity of metals in microorganisms

IV. Cytogenetic aberrations induced by metals in tissue culture cells

V. Induction by metals of neoplastic transformation of tissue culture cells

Vi. Nuclear uptake of metals in vivo and concomitant inhibitory effects of metal on synthesis of nucleic acids.

However no definite mechanisms were proposed by Sunderman.

In a preliminary examination of a possible mechanism for the carcinogenic action of arsenic, the present authors (to be published 1981) noted that (1) arsenic inhibited DNA repair and (2) in every case, that could be checked, disturbances in the metabolic balances of copper and sulfur had occurred. (It should also be noted that the rat should not be used as an animal model because its metabolism is totally different from humans). Thus it seems likely that arsenic is not an initiator and may require co-carcinogens for carcinogenic action in human.

Further work needs to be done to establish a detailed mechanism for the action of arsenic. In addition the mechanisms for nickel, chromium and cadmium need to be proposed. If beryllium is proved to be a human carcinogen its mechanism will also be required.

In order to compare the hazard of the burial of elements with that incurred by the burial of low level radioactive wastes the following needs to be done: -

1) Estimates of the amounts of trace elements (above normal background) likely to find their way via aquatic and soil sources into the human food and drinking water chain from burial sites.

2) Estimates of the increases of trace elements likely to be absorbed by critical populations living near burial sites.

3) Mechanisms of action which may lead to human tumors particularly for arsenic, nickel, cadmium and chromium.

4) Hence determine threshold levels (which must exist for essential elements) for arsenic, nickel, cadmium, and chromium, as well as critical organ levels (organs in the body most likely to host tumors).

5] From this information compare the hazards incurred from the burial of arsenic, nickel, cadmium and chromium with that from low level radioactive substances.

and 6) Taking the four elements listed, as models, estimate the risks which might be incurred from the burial of other elements, such as

lead. However, it should be noted that carcinogenicity may not be the highest priority concern for such metals as lead. In that instance teratogenicity and other effects all would have a higher priority when considering overall health.