ENVIRONMENTAL CARCINOGENS *)

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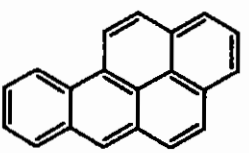
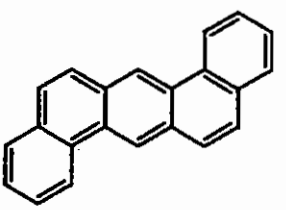
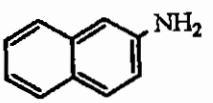
It is now more than 200 years since the first observation that chemical substances c cause cancer. The English physician Percival Pott noted that chimney sweeps suffered fror relatively scrotal cancer and he reasoned (correctly) that this was to their exposure to soot. It not until the 1930's that chemicals responsible for this condition were identified.

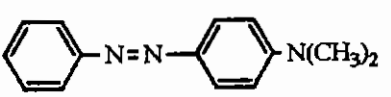
They were polycylic aromatic hydrocarbons (PAH) benzopyrene and dibenzanthracer

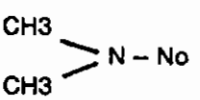




As modern industry developed it was noted that workers in certain chemical fact suffered from unusually high incidences of various kinds of cancer and after considerable ir tigations the chemicals responsible were identified. These include,

Aromatic amines eg.  bladder cancer, dyestuff industry

Azo dyes eg.  liver cancer, dyes and textiles

Nitrosamines eg.  Rubber industry

Organochlorine Compounds	eg.	CCl_4	Dry Cleaning Industry
		$CH_2 = CH - Cl$	P.V.C. factories (both liver cancer)

It is now generally accepted that a considerable proportion of human cancers can be attributed to exposure the chemicals present in food, water, the atmosphere and in the work place. The percentage of cancers attributed to chemical carcinogens is a matter of controversy but some medical authorities consider that up to 80% of human cancers may be caused by carcinogens. Even if the figure is considerably less it is still an extremely important health issue.

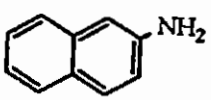
The invertigation of chemical carcinogenesis has several aims :

1. To identify chemical carcinogenesis that cause human cancer.
2. To find out how such chemicals are formed and how they are distributed in the environment and in what quantities.
3. To control the formation and release of carcinogens into man's environment.
4. To safely dispose of waste chemicals which are carcinogens.
5. To study the mechanism of the induction of cancer by chemical carcinogens in the hope that this knowledge will help to find cures for the disease.

The leading authority on chemical carcinogens is the International Agency for Research on Cancer, located in France and a branch of the World Health Organization. The Agency surveys all reports on carcinogenic chemicals and eventually if it conciders the evidence strong enough lists the material as a carcinogen. It should be noted that although many hundreds or oven thousands of chemicals heve been certified as carcinogens by the Agency.

The status of a chemical as a carcinogens is indicated in three levels of biological activity:

I - Know to cause cancer in humans eg.



II - Know to cause in animals, suspected of causing cancer in humas e.g. chromates

III - Suspected of causing cancer in animals eg. arsenic saltd

The above classification is based on the available information and is not a measure of carcinogenic effects in a quantitative sense.

The potency of carcinogens varies enormausly through at least 6 orders of magnitude. Some axamples are given below.

Arbitraty Scale of Carcinogenic activity	1	-- Chlorofrom
	10	-- Trichlorethylene
	100	-- - Naphthylamine
	10^3	-- Dibromochloropropane
	10^4	-- 3 - Methylcholanthrene
	10^5	-- Sterigmatocystin
	10^6	-- Aflatoxin B1

It is interesting to note that the most dangerous carcinogens are natural product and man-made chemicals. Obviously the potency of a carcinogen dictates the amount require cause the disease, with more potent carcinogens affective at very low levels.

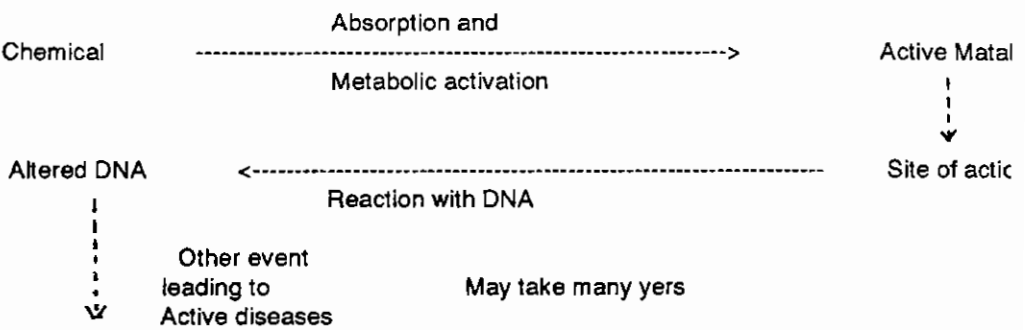
Activity of Carcinogens

The main difficulty with carcinogens is that they act very slowly requiring years a exposure before active disease can be detected. The other problem is activity at low levels, trace amounts are required.

According to some experts there is no safe dose of a carcinogen therefore no safe level in a f drink or ini the environment.

Others hold that even for carcinogens there is a threshold level below which no dam to health will occur. However at present we do not have enough information to set safe level carcinogens therefore all efforts must be mede to limit human exposure as much as possible.

Most chemical carcinogens are not themselves active but require bioactivation in body. This involve one more metabolic steps converting the original compound into the activ ultimate carcinogen.



Most carcinogens are known to act chemically with DNA forming cehmical deriva which interfere with the usual 1-1-bonding found in DNA. This interupts the base pairing hence the replication of DNA is disturbed leading to the formation of DNA which is not true c original strend. If the alteration is at a gene controlling cell division the result may be a cance cell.

Some dfence against carcinogens is found in the body. These are repair mechan which recognize abnormal DNA, cur it out and replace it with the correct sequence. Thes also antibodies produced by the immnune system which recognize abnormal cells, attack and kill them. Although carcinogen may set off the carcinogenic process the active deseas quires othe factors which are presently not fully understood.

Chemical Carcinogens in the Environment

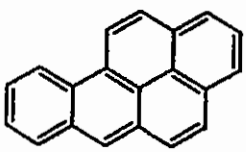
It has been found that carcinogen are widwspread in our environmwnt being pres food, drinking water, the atmosphere and in the soil. Carcinogens can be divided into man- chemiscals and natrurally occuring chemicals but some are both natrurally and man- made. I section we will consider some importtant type which are considered to be hazardous to h health.

1) **Polycylic Aromatic Hydroccarbons (PAH)**

These compounds are ubiquitous, being products of incomplete combustion of any kinds of organic materials. Sources are car ezhausts, factory chimneys, incinerators, buring of rubbish or vegatation, natural forest fires etc.

There are many PAH's but only some are carcinogenic. The best known benzopyrene (BP) is the one which is usually used as an index of carcinogenicity. When analysing materials for PAH it is normal to analyze for BP and quote the level of this as our measure of carcinogenic potential of the material.

BP



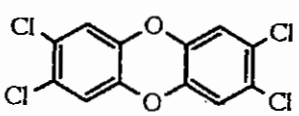
BP occurs in smoke, soot, oil, air, water, food etc. It is a significant air pollutant in city air and is a possible hazard in smoked foods. It is also one of the principal carcinogens in cigarette smoke.

Since BP levels are normally low (ppm-ppb) extremely sensitive methods of analysis are required. Succesful methods include GLC/MS, HPLC using fluorescence detector, however it is not the purpose of this lecture to deal with analytical details.

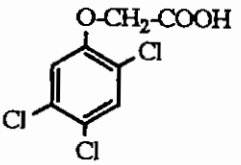
Measures of control to limit exposure to PAH's are catalytic converters in cars (promotes complete combustion), methods of cleaning dischanges from chimneys of power station, limiting smoke content of fodds and cutting down on smoking.

2) **Dioxins**

The term dioxin refers to a group of compaunds, which are chlorinated dibenzodioxins, the best known of which is tetrachlorodibenzodioxin (TCDD).



Dioxins were first discovered as impurities in the auxin like herbicides (Mainly, 2,4,5-T), and explained the unexpected toxic effects of these compounds.



Studies showed that TCDD was the most toxic synthetic compound knoown and its l 50 for the guinea pig was a record low of 0.0006 mg/kg, it is about one million times as toxic 245T. TCDD was also found to be teratogenic, mutagenic and carcinogenic.

Recent studies have shown that TCDD is now a widespread environmental carcino as there are several sources of formation.

* Impurity in herbicides
* Formed by burning plastics
* Formed in the manufacture of chlorinated compounds such as chlorophenol disinfectants
* Formed in the manufacture of paper products (from use of chlorine bleaches to whiten paper)

As a result TCDD and other chlorinated isomers (Dioxin) have been found to be present

1. City air
2. Agricultural soil
3. Garbage dumps
4. Tivers and lakes
5. Paper products
6. Food, meat, milk and daily products, fish etc.

Generally dioxins are present only at PPb levels and require sensitive analytical m ods, mass spectrometry is the method of choice.

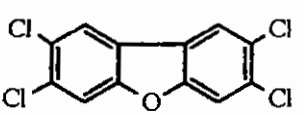
The role of dioxins as environmental carcinogens is a matter of great controversy governments are under great pressure to limit their formation and spread in the environment.

Measures now taken in some countries.

1. Forbidding manufacture of herbicides containing dioxins.
2. Banning other chemicals contaminated with dioxins.
3. Control of burning of waste material.
4. Regulation of the design of incinerators. 5. Control of paper mills (limits ti toxic waste).

Associated with dioxins are chlorinated dibenzofurans (known incorrectly as furans).

eg.



These are formed from the same sources and are considered to have similar toxic and carcinogenic properties.

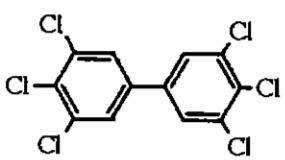
3. Polychlorinated biphenyls or Polybrominated biphenlys (pcB's, PBB's)

Polychlorinated biphenyls were manufactured for many years and had numerous industrial uses. The most important use was as an electrical insulating fluid for filling transformers and in other smaller electrical appliances.

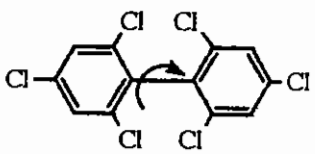
PCB's are liquids or waxy solids composed of a mixture of chlorinated isomers. The fact that they are such complex mixtures (usually more than 50 isomers) makes assessment of toxic effects difficult.

However it is well known that like dioxins they are very stable and accumulate in the environment. At present there is no satisfactory way of getting rid of them. They eventually contaminate the food chain and accumulate in the human body. It is claimed that they cause skin disease, liver disorder, nervous damage and are carcinogens.

Isomers with planar configuration (eg. A) are thought to be much more toxic non-planar isomers (eg. B), since former can possibly interculate with DNA readily.



planar



non-planar, steric of atoms causes rotation about the C-C bond joining

The role of PCB's (and the associated PBB's) as environmental carcinogens is still being evaluated. It has even been suggested that any carcinogenic effects of PCB's are due to dioxin contaminants, but this theory has not been substantiated.

4) Chlorinated Compounds (Sometimes referred to as Trihalomethanos)

In the past 20 years seem common chlorinated organic solvents have been found to be highly toxic and to have carcinogenic properties. Carbon tetrachloride, a former dry-cleaning solvent is now restricted in use and chloroform an agent used as an anaesthetic and ingredient of caugh mixtures and toothpaste is also banned in many places. Suspected of carcinogenic activity are also dichlorometane trichloroethylene and tetrachloromethane. Vinyl chloride is an established carcinogen.

The industrial use of all three materials is now strictly controlled but scientists were alarmed ti find that some of these compounds (eg. CC14 and CHC13) are found in drinking water supplies.

The source has been traced to the process of chlorination of public water supplies to sterilize them. All natural water contains organic compounds leached from the soil and during the

chlorination various reactions accur between chlorine and the constituents of water. Eventua CCl4 and CHCl3 may be formed and they have been found in drinking water in many parts of tl U.S.A. and Europe in Ng/L levels (ppb).

Organic Compounds from soil —Cl2—> Chlorinated derivatives —decomp—> CCl4+CHCl3+CH2Cl2 etc.

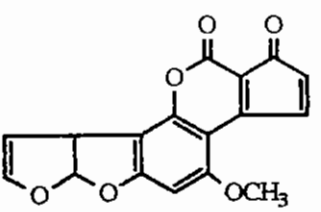
The analytical method used to measure halogenated compounds in water is GC wi ECD.

Proposed control mathods include; lower chlorine levels; alternative sterilization tec niques eg. 0_3.

Other sources of organochlorine carcinogens inwater and air are from industrial was damps and evaporation in factory processes.

5. Carcinogenic mould metabolites

The discovery of the aflatoxins in 1960 focussed attention on toxic mould metabolite Food is a good medium for mould growth and mouldy food can contain the various metabolit produced by fungi. The aflatoxins were the first molud metabolites found to be carcinogenic a suprisingly they were estimated to be the most potent and dangerous carcinogens knwon.



The alfatoxins (4 main compounds B1, B2, G1, G2) cause liver cancer and are consi ered to the main cause of liver cancer many African and Asian countries. The mou *Aspergillus flavus* is common and Aflatoxins have been found as contaminants in many foods a drinks especially nuts. They have also been found in milk and dairy products.

Since the mould grown best in hot humid climates then tropical food supplies are mc cantaminated. Obviously the conditions are right for aflatoxins to be a serious health hazard Indonesia.

Aflatoxins are chemically very stable and cannot be removed from foods or destroyed cooking.

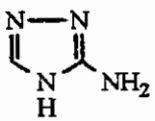
Aflatoxins may be analyzed in foods by fairly simple prodessed because of their ch acteristic intense fluorescene. A suitable solvent extrat is made and after an appopriate clean- the aflatoxins may be detected and quantitates by a TLC fluorescence method. This assay c detect aflatoxins at ppb levels.

Following the discovery of the aflatoxins much research has been carried out on mou metabolites and several other carcinogens have been found derived from other common fur growing on crops and stored foods. This is an interesting area of research combining chemist biochemistry, microbiology and analysis. There are probably many more mould carcinogens to

found in foods and no doubt mould carcinogens represent an important public health problem in Indonesia. Good storage and food processing is the best approach to the solution of this problem.

6) **Pesticide Residues**

There is much controversy about the carcinogenic affects of pesticides. It has often been claimed that DDT is carcinogenic and some authorities list it on such however the IARC has not concluded that DDT is a carcinogenic. Other pesticides have been identified as pesticides. Chlordane, heptachlor and dieldrin are animal carcinogens and the herbicide amitrole has been listed as a carcinogen by the US EPA.



The general population is exposed to pesticides mainly through food alrhough traces may also be found in water.

The great variety of pesticides requires all possible analytical techniques and pesticide analysis is a highly specialized area of analytical and food chemistry.

Elimination of carcinogenic pesticides and more careful control of the use of pesticides is the way to limit this problem.

7) **Dangerous food additives**

Approved food additives have been shown to be safe after long term toxicity amounts of nitrite and nitrate (from carcinogenic nitrosamines in food) coumarin, and various artifical flavours.

The analytical examination for dangerous food additives is an important task for a food analysis labotory.

In particular the nitrosamines have given great cause for concern. Nitrosamines are easily formed in foods by the interaction of nitrite with secondary amines in an acid medium. Nitrite is a constitnent of some vegetables and is also used a preservative for meals. Secondary amines are present in meat fish, cheese and other common foods. The formation of nitrosamines may accur slowly in the foods or more rapidly in the acidity of the stomach.

This is not a mehcanism, HONO is not the nitrosating species.

Nitrosamine formation is catalyzed by thiocyanate ion and some other species but is inhibited by ascorbic acid and thiols, so the whole diet has to be examined in the study of nitrosamine carcinogenesis.

Nitrosamine are certainly potent carcinogens and animals can induce human in many body organs.

The question is, on the amounts present in foods and likley to be formed in the body

sufficient to cause the disease and the answer at present is that we have insufficient informati to make a decision.

8). **Carcinogenic Metals**

Salt and simple compounds of some metallic elements are also carcinogenic. Epic miological studies and animal tests have shown thata compound of As, Cd and Cr are probal carcinogenic to humans.

All these common metallic compounds are important commercial material and have wi use in industry. Partly as a result of industrial use and partly due to natural occurance su compounds are widely distributed in the environment carcinogens.

:As : As compouds are used as pesticides and are present in fertilizers.
As containing copounds are dumped as industrial wastes.
As compound can contaminate foods, water and air near metal smelting plants.

Cd : Cd compounds are impurities fertilizer and are release into the environment by mining and smelting processes.
Cd compouds are found in foods, especially fish and shell fish living in polutec waters.

Cr : Cr compouds are important for leather lanning, electroplating, and printing. Cı wastes are dumped in sewers and waste depots, but the Cr is leached out may get into the food chain.

Carcinogenic metals can readily be assayed by AA and atomic emission spectrosco which are capable of detecting the low levels in foods and water.

CONCLUSIONS

In this short lecture it has not been possuble to cover all the main types of chem carcinogens presently known.

It is clear that chemical carcinogens present in the environment (air, water, soil, food a workplace) represent a significant hazard for man and are probably responsible for a considera proportion of human cancers.

Hopefully with further research we will be able to avoid the use of the most danger carcinogens and by the control of pollution and the proper disposal of chemical wastes we will able to reduce the burden of chemical carcinogens in our environment. It should then follow t the incidence of cancer in the community should decrease.