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PLENARY MEETING OF BIT CHLORE

0000323

On June 15, 1979

SORRENTO - ITALY

# CHLORINATED ORGANO-COMPOUNDS AND ECOLOGY



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# CHLORINATED ORGANO-COMPOUNDS AND ECOLOGY

Between the chemicals those most directly involved in pollution problems are the chlorinated-organic compounds. They include the chlorinated aliphatic and aromatic hydrocarbons which are almost exclusively produced in industry. About thirty chlorinated-organic compounds are known, among which griseofulvin, drosophilin, and caldariomycin, which are of natural origin, metabolites of mycetes, however they are of no importance from an ecological point of view.

Instead, certain synthetic chlorinated-organo-compounds like insecticides (for example aralkanes and cycloalkanes), herbicides (like phenooxyacetics) and fungicides (like hexachlorobenzene and pentachlorophenol) are of great importance.

These compounds represent, from a certain point of view, the paradigm of environmental pollution from chemical compounds. Their characteristic is a pronounced biological activity and a great stability in time, for which they have become dangerous even for man.

There are also the chlorinated aromatics which include the chlorinated naphtalenes, chlorinated biphenyls, chlorinated phenodioxanes and chlorinated phenolic furanes, highly toxic substances which can also be found in wild animals as the last link of the food chain.

In ecology, the most important is DDT, which like chlorinated biphenyls, is already spread in large quantities in the atmosphere, in the hydrosphere, in the upper parts of the lithosphere and in various living organisms. These compounds are also particularly characterized by their chemical stability in that they are subject

to a slow biodegradation calculated for same as 20 days to 2 years to degrade by 50%. Their metabolites, which often have an affinity with the initial products, tend to accumulate in the hydrosphere, which is, as we know, an important source of food for humans and plays a fundamental role in enriching atmosphere with carbon dioxide.

Even though these compounds are of great ecological importance, we are mainly interested in the aliphatic chloro-compounds among which:

- methyl chloride, methylene chloride, chloroform, carbon tetrachloride, trichloroethylene, the 1,2-dichloroethane, perchloroethylene, vinylidene chloride and vinyl chloride. Today they has been produced in large quantities and they are characterized by various toxicity levels. Some have long life in biological and abiotic systems and can accumulate in living organisms in dangerous concentrations. For others, it is not possible to quantify the real risk that they represent for man since there is no agreement on some of their toxicological characteristics.

If we examine the 9 listed compounds we can see that at least 6 of them are commonly considered carcinogens: they are vinyl chloride, vinylidene chloride, chloroform, carbon tetrachloride, 1,2-dichloroethane and trichloroethylene.

But only for vinyl chloride can we really speak of a carcinogenic risk for man. For the others we can only make assumptions and await proof.

In the case of trichloroethylene, carcinogenic activity has been denied at various times due to data falsified by the presence of impurities.

In any case for a complete comprehension of the problem it is necessary to reflect on certain fundamental concepts of modern carcinogenesis.

Until a few years ago, experimental cancerology was restricted to a limited number of specialists. Today it interests the whole chemical industry because of the pollution problem that involves work environment, territory, consumer.

We have known for a long time that some chemical substances can cause cancer. In 1775 PERCIVAL POTT described a type of skin cancer found in chimney-sweeps due to the tar found in mineral coal. In 1916 two Japanese, YAMAGIWA and ICIKAWA, confirmed this discovery reproducing skin cancer in rabbits by repeated brushings of tar. The active principle was brought into evidence in 1930 by COOK and CANNAWAY who had isolated benzopirene, a highly carcinogenic polycyclic hydrocarbon.

In 1895 REHN showed the carcinogenic action of aromatic amines on the urinary system of workers in dye and rubber factories, opening new prospects in research. The most dangerous proved to be benzidine, 2-naphthylamine, 4-aminodiphenol.

In the course of time many other substances derived from carbon, from schist, from petroleum, from tiourea, from azo dye, nitro compounds, products from the combustion of tobacco, aliphatic hydrocarbons, asbestos, arsenic and chrome were added. It is interesting to remember that in 1941 carbon tetrachloride was noted to be carcinogenic for animals and that in 1945 even chloroform demonstrated to have the same effect on mice.

In 1958, HADDOW, observing that the study of viruses as a potential cause of human tumors hadn't brought concrete results,

made the assumption that chemical substances could be a principal cause of tumors. This idea became accepted by scientists who from then on, began to think that the majority of human tumors was brought on by chemical compounds.

But the problem exploded in 1974 when vinyl chloride was demonstrated to be carcinogenic even for man. It was a year of great fear because not only industries but also sanitary and governmental organizations of all the industrial nations were unprepared.

The reason for the resonance of this discovery may be found in the fact that this substance was considered safe, that many people had been exposed to it, and that the substance was very active on animals, therefore, it was feared that a great number of tumors would have appeared in man, too.

Years of vast scientific programs, medical and technical meetings and research committees followed. The main program requested was to prepare a list of all carcinogenic substances. In this period much effort was given to scientific research. We learned that various substances, among which some chloro-compounds, actually had a carcinogenic effect. Five years later the problem is to come near a static period mainly because of a methodological crisis in basic research.

Some thousands of substances have been studied to evaluate their carcinogenic power. According to information from the National Cancer Institute, of the 7.000 compounds tested more than 1.000 revealed some carcinogenic action. Since 1972, in the International Center of Cancer Research in Lyon, there has been a critical revision of studies on suspected substances. Until 1977, 368 chemical substances had been examined. For 26 of them a

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direct relationship between exposure to the compound and appearance of malignant tumors in man was documented (table 1).

It was noted that about 221 compounds were able to produce malignant tumors in animals but it hasn't been possible to quantify the risk that they represent for man because, as mentioned in the article, direct observation on man and adequate epidemiolgical research doesn't exist.

These results are fundamental to the understanding of present the state of research on carcinogenesis. The critical point lies in the difficulty of the extrapolation to man.

It has been said and recently confirmed that malignant tumors in man derive from environmental factors in 80 to 90% of the cases, meaning with this expression factors that are part of our way of life, of eating, of working, our vices and all the biological and natural agents that surround us.

In the recent past the expression "environmental factor" was interpreted and used in the wrong way and had become synonymous with environmental pollution due to industrial development. For this reason the majority of tumors were attributed to the chemical industry. Today this error has been corrected.

An effort has been made to try to define the number of tumors directly connected with occupational factors. While some assume that they are from 1% to 5% of the total number of all tumors in man, the National Cancer Institute has increased this percentage for the USA, up to 20% according to an estimate that is shown in the annexed table 2.

These figures leave us perplexed even if they refer to a highly industrialised country like the USA. We know how important certain

compounds present in food or some natural products like micotoxin or substances of vegetable origin like cycasin are in the genesis of cancer. We should not forget the importance of tobacco, alcohol, viruses and many other factors which are not yet well known.

In the northern regions of China cancer of the esophagus is common in both the population and domestic animals. In Vietnam cancer of the liver is very common even in children a few months old, which shows the importance of certain environmental factors.

Today it is said almost 60.000 chemical compounds exist on the world market and that every year new molecules are synthesized by industry. There seems to be toxicological information on only 20.000 substances and carcinogenic studies on about 3.000.

The estimates are therefore always rather approximate and we are very far from a reasonable control of the situation.

An important effort in this direction is being made in the USA with the Toxic Substance Control Act (TOSCA) for the purpose of making an inventory of the chemical substances in industrial use. The list of these substances will be added to the pharmaceutical, food additives and pesticide lists, in order to make it possible to develop research programs on the toxicological characteristics of all these substances.

The realisation of this vast project, comprising the creation of new organizational structures and the investement of large amounts of capital, will encounter many difficulties for the lack of knowledge that we still have on the biological problems concerning cancer.

The necessity of extending our toxicological knowledge to the largest possible number of chemical compounds is beyond doubt,

but we can't hide the practical difficulties of developing this program in all the industrialized countries, and in particular in Europe. Information on the carcinogenic effect of substances is obtained mainly from 3 types of research:

1) Short term tests
2) Longt term tests on animal
3) Epidemiological studies

The goal of short term tests is to study the mutagenic activity of substances. They can be used as quick tests for an initial approach to the carcinogenic activity of the compound. For this purpose, a series of tests is used to completely examine the various biological aspects of the problem.

For long term tests there is some agreement on the procedures to follow,on the type and number of animals to use, on the length of the treatment, and on the ways of introduction of the substance. Some researchers insist on the necessity of using well-selected and well-known laboratory animals, for which the type and number of tumors that can develop spontaneously is known. However this requirement is only one aspect of a good experiment. Difficulties occur when we must evaluate, even in a qualitative mode, the results of an experimental investigation. There can be difficulties in the interpretation of the malignancy of the observed tumors, in the evaluation of their incidence and even in the evaluation of the meaning of the experiment, due to the type of animals, the dosage and the methods of introduction.

For this reason we should not forget that a large part of

carcinogens do not act directly on the organism but act through their metabolites that produce in the target cells an alteration of their control mechanism. We then have a modification of the genome or of other molecular mechanisms that form new types of modified cells which constitute the base of the tumor.

The initial molecular damage is always very limited and is conditioned by the presence of promotional factors, by the conditions of defense of the organism and by hormonal conditions.

There is no universal reaction to carcinogens. Every species of animal, every individual has his own particular receptivity that, in most cases, is related to the transport and metabolism of the carcinogen as well as to the intensity of effect that each substance has at cellular level. Therefore we must add to the long term investigations metabolism tests of the substance, both in man and in experimental animals, as well as tests of pharmacokinetics to accurately determine the intensity of the effect.

The positive results of a long term study on animals can have a predictive meaning for man only if the metabolism of the substance is identical in both man and test animal.

If this is not so, the extrapolation to man is useless we would be studying the action of a substance which will never be produced inside the body as a consequence of the introduction of a certain compound.

It is therefore difficult to get an objective qualitative evaluation on the results obtained from laboratory animals. The cancer expert can determine the existance of sufficient evidence of carcinogenicity in animals for a particular substance, but these results can not be directly extrapolated to man.

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The hypothesis of risk for man can be advanced only if metabolic identities exist, if the experiment has been conducted on various types of animals, and a sufficient number of organs react to the carcinogenic stimulus of the compound. However a scientific demonstration of a real carcinogenic risk for human beings can only be based on epidemiological studies. The previously mentioned work of the IARC is an example.

A quantitative extrapolation of risk can not be made by comparison between animals and man as was correctly put into evidence in the 1977 Drinking Water and Health of the National Academy of Sciences, due to the different absorption of chemical compounds, body distribution, metabolism, excretion and reabsorption, different interference of the bacteria of the digestive tube, the difference of the molecular receptor of the carcinogen and the cellular sensibility and reactivity, as well as for the genetic and environmental difference of various animals.

The impossibility of direct extrapolation of the experimental data to man makes it necessary to conduct epidemiological studies even if they can be falsified by an insufficient number of cases, by a reduced period of exposure, by multiple exposures and an insufficient knowledge of the exposure. The fact that the epidemiological studies can be considered only for the substances already in use, reduces their field of application but not their importance.

In 1975 the BIT organized a meeting of experts to study the problem. At that time the following difficulties of extrapolation to man were noted: a greater heterogenicity, a greater variety of exogenous and endogenous factors, a greater dispersion of age,

a more fractioned exposure, the exposure to more carcinogens or cocarcinogens and the difference in metabolism.

These problems inevitably lead us to question the existence of safety limits. This point could be partially solved if we were not so anxious to find a mathematical demonstration of the absence of risk at lower concentrations and if we were satisfied with the evidence of the existence of doses "without effect" which is completely different from doses "without risk".

As an example ROE cites the man who has the habit of smoking only cigarette a day. This vice will not particularly increase the incidence of lung cancer, therefore we can consider this a minor risk. ROE also stresses the error that is continually made in trying to classify substances as carcinogenic and non-carcinogenic noting that it would be more logical to make a scale of values from 0 to 100 of the risk that a compound can represent for man.

From what has been said we can understand that science is anxiously looking for a solution to the problem.

A group of researchers of the American Scientific Agencies of OSHA, developed a philosophy according to which human life is too valuable to be put into danger, therefore any exposure to suspected carcinogenic substance, that is, substances that have revealed their effect solely on animals, should be eliminated.

It is a point of view that can have its positive, even if questionable aspects, but we can not help observing that the concept of carcinogenic substances in animals has been identified with the concept of carcinogenic substances in man, which is not true.

On this basis OSHA issued a group of proposals while awaiting

adequate laws. The American Industrial Health Council (AIHC), confiding in a modification, refused these proposals, defining them: scientifically not acceptable, legally dishonest and economically not applicable.

- The creation of a committee of experts, chosen by the National Academy of Sciences, has been proposed. Its task is to determine, on the basis of existing data, which substances are really carcinogenic for man and how much of a risk they represent for humanity.

- More importance should be given to the negative results of epidemiological research on human populations than to the positive results obtained on laboratory animals. In other words, by completely reversing the proposal of OSHA, we can reaffirm the concept that only an epidemiological research on man can give us the certainty of the carcinogenicity of a substance.

- The results of long term experiments on animals are insufficient to define the risk of cancer for man of a chemical compound because the direct extrapolation of the results is scientifically impossible.

- The tests of mutagenesis, and in general all short-term tests, are inadequate to predict if a substance is carcinogenic for man.

- We can not support the concept of zero risk because we do not and we can not have a society without risk. It is therefore useless and above all detrimental to issue laws aiming at this principle. A limit value, which necessarily implies an acceptable level of risk, must be defined for every product.

- The danger of potential carcinogens will have to be

evaluated on the basis of threshold limits.

- When evaluating safety in industrial plants we must consider the possibility of using individual protection equipment.

- The small quantities of carcinogens contained in mixtures must be excluded from regulations, if they are very limited, because the idea that even one single molecule can originate tumors should be considered obsolete.



It will not be easy to make these principles universally accepted but the majority of researchers are agreeing more and more with them, because they lead to a practical solution of the problem. This is more important than the study of inapplicable laws, such as the DELAUNAY law.

We are all convinced that man is the target of a large quantity of carcinogenic factors, however we also know that the body has learned to defend itself and remains a victim of cancer when its defense mechanism fails or when the quantity of "Noxa" is in excess. We agree on the fact that the study of experimental carcinogenesis is necessary, even indispensable to obtain precious information for prevention but the results of these studies can not be directly extrapolated to man.

The information obtained from short and long term tests and from epidemiological studies must be correlated to quantify the risk which has to be analyzed substance by substance.

It has been demonstrated that for many compounds doses without effect exist and we believe that this is the right attitude because human activity with zero risk does not exist.

We agree with the affirmation that life is too precious to

be wasted uselessly,but we are aware of the fact that there are some realities which we must face objectively, without illusion, with courage and with an open mind.

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Table 1 Chemicals or industrial processes associated with cancer induction in man — target organs and main routes of exposure

| Chemical or Industrial Process | Main Type of Exposure [1] | Target Organs Man | Main Route of Exposure [2] |
|---|---|---|---|
| 1. Aflatoxins | Environmental, occupational [3] | Liver | Oral, inhalation [3] |
| 2. 4-Aminobiphenyl | Occupational | Bladder | Inhalation, skin, oral |
| 3. Arsenic compounds | Occupational, medicinal and environmental | Skin, lung, liver [4] | Inhalation, oral, skin |
| 4. Asbestos | Occupational | Lung, pleural cavity, gastrointestinal tract | Inhalation, oral |
| 5. Auramine (manufacture of) | Occupational | Bladder | Inhalation, skin, oral |
| 6. Benzene | Occupational | Haemopoietic system | Inhalation, skin |
| 7. Benzidine | Occupational | Bladder | Inhalation, skin, oral |
| 8. Bis(chloromethyl)ether | Occupational | Lung | Inhalation |
| 9. Cadmium using industries (possibly cadmium oxide) | Occupational | Prostate, lung [5] | Inhalation, oral |
| 10. Chloramphenicol | Medicinal | Haemopoietic system | Oral, injection |
| 11. Chloromethyl methyl ether (possibly associated with bis(chloromethyl)ether) | Occupational | Lung | Inhalation |
| 12. Chromium (chromate producing industries) | Occupational | Lung, nasal cavities [5] | Inhalation |
| 13. Cyclophosphamide | Medicinal | Bladder | Oral, injection |
| 14. Diethylstilboestrol | Medicinal | Uterus, vagina | Oral |
| 15. Haematite mining (?radon) | Occupational | Lung | Inhalation |
| 16. Isopropyl oil | Occupational | Nasal cavity, larynx | Inhalation |
| 17. Melphalan | Medicinal | Haemopoietic system | Oral, injection |
| 18. Mustard gas | Occupational | Lung, larynx | Inhalation |
| 19. 2-Naphthylamine | Occupational | Bladder | Inhalation, skin, oral |
| 20. Nickel (nickel refining) | Occupational | Nasal cavity, lung | Inhalation |
| 21. *N,N*-Bis(2-chloroethyl)-2-naphthylamine | Medicinal | Bladder | Oral |
| 22. Oxymetholone | Medicinal | Liver | Oral |
| 23. Phenacetin | Medicinal | Kidney | Oral |
| 24. Phenytoin | Medicinal | Lympho-reticular tissues | Oral, injection |
| 25. Soot, tars & oils | Occupational, environmental | Lung, skin (scrotum) | Inhalation, skin |
| 26. Vinyl chloride | Occupational | Liver, brain [6], lung [5] | Inhalation, skin |

TABLE 2

| Substance | Number of workers exposed | Risk rate | Number of tumors / year |
|---|---|---|---|
| Arsenic | 1.500.000 | 3-8 cr lung | 2.100-7.300 |
| Benzene | 2.000.000 | 2-3→7 leukemia | 240-1.400 |
| Tar | 60.000 | 2-6 cr lung, larynx, skin, scrotum | 160-800 |
| V C M | 2.260.000 | 200 and 1,9 respectively for angiosarcoma, brains, lung | 1.940 |
| Chrome | 1.500.000 | 3-40 cr nose, breasts, lung, larynx | 2.400-46.000 |
| Iron oxide | 1.600.000 | 2-5 cr lung and larynx | 1.300-5.000 |
| Nickel | 1.370.000 | 5-10 cr lung | 3.800-5.000 |
| Petroleum derivatives | 3.000.000 | 2-6 cr lung, larynx | 2.400-12.000 |
| Asbestos | 4.000.000 | mesothelioma, cr lung, and gastrointestinal | 67.000 |