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Dioxins: analytical chemical aspects of the problem

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ABSTRACT. The dioxins are a large set of polyhalogenated polycyclic compounds formed as impurities during many types of production using chlorine, bromine and their compounds. These xenobiotics have no equals among other contaminants in their danger to man and in global ecological effects. The current status of some aspects of the problem of dioxin and related compounds is considered using material from the foreign scientific press. Data are presented on the physicochemical and other properties of dioxins. Information is correlated on the main sources of dioxins and on the methods of determining them in the environment and the biosphere (air, soil, water, biological samples, etc.). Problems considered are the contamination of the environment, monitoring, ways of reducing the danger and the prevention of dioxin contamination.

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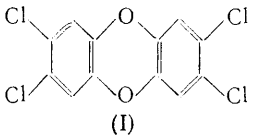
I. Introduction

In the last 15–20 years, one more ecological hazard has been added to the vast total threatening civilisation, viz. the possibility of planetary poisoning of our habitation by dioxin and compounds related it.[1–114] Dioxin and the numerous group of dioxin-like substances are foreign to the living organism (xenobiotics) and enter the biosphere from the production or discharges of numerous technologies. In contrast to the mass of other xenobiotics such as organochlorine pesticides *dioxins are never the desired product* of human activity. They only accompany it as microimpurities.[50] Consequently the negative actions of dioxin microimpurities on the living matter of the planet remained unnoticed against the background of the action of thousands and millions of tons of other technogenic discharges for many decades. However this dioxin microimpurity, characterised by a complex of unusual physicochemical properties and unique biological activity, may become a source of the most dangerous lasting contamination of the biosphere, significantly more serious than its contamination by many other substances such as the organochlorine pesticides.[94]

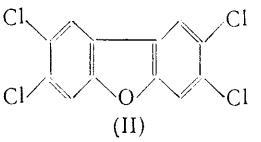
This is because in the last 50–60 years dioxins and related compounds have been generated continuously and on ever increasing scale by civilisation, discharged into nature and have accumulated there. The process of accumulation of these xenobiotics in the biosphere knows no saturation limits or national boundaries. At the present time the situation is such that the concentration of dioxins in the hydrosphere and lithosphere may reach critical values and disease of living matter may assume an irreversible character.

The history of the 'acquaintance' of mankind with dioxins arose in 1930 when the development of the manufacture and use of polychlorophenols led to an increase in the *occupational disease chloroacne* (relapsing inflammation of the sebaceous glands), although the illness itself had been known since 1899.[50,88–93] The geographical distribution of chloroacne spread significantly in 1940–1950 linked with the creation of large tonnage manufacture of 2,4,5-trichlorophenol and also of the manufacture of the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) obtained from it, of the antibacterial preparation hexachlorophene, etc. Many cases of poisoning of personnel in this industry during operations have been described, some as a result of accidents.[17,38,88] It has recently been shown that recurrences of chloracne in many of those affected have developed even 20–35 years after the disease.[90]

The source of these diseases was established in 1957 by several groups of investigators simultaneously.[115–117] It turned out to be 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) (I) formed as a microcontaminant when making 2,4,5-trichlorophenol (TCP).[115–116] Passing with the latter into technological chains and then into the final product (herbicides, antibacterial preparations, etc.) dioxin (I) sets in motion, as clarified recently, not only the disease chloracne, but also others including acute poisoning.[93,118,119]



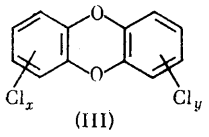
(I)

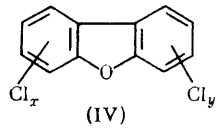


(II)

2,3,7,8-Tetrachlorodibenzofuran (2,3,7,8-TCDF) (II) was also postulated, simultaneously with dioxin (I), as a chloracnogenic factor.[117] However particular attention has been drawn to this xenobiotic itself as a microcontaminant in polychlorobiphenyls (PCB) used as liquid dielectrics, heat-transfer agents, hydraulic fluids, etc. The massive poisonings caused by xenobiotic (II) (in 1968 in Japan[120] and in 1979 in Taiwan[121]) were linked with the entry of PCB into rice oil which led to the so-called Yusho illness (acute liver poisoning acocmpanied by many side effects).[95,96]

It has been shown that xenobiotics (I) and (II), like many other examples of polychlorinated dibenzo-*p*-dioxins (PCDD) (III) and dibenzofurans (PCDF) (IV), have similar toxicological characteristics.[122]

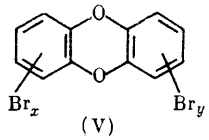

(III)

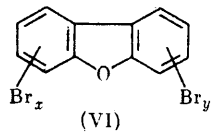

(IV)

$n = x + y = 1$ to 8

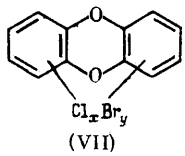
The presence of micro contamination by (III) and (IV) in the products of chloro-compound manufacture is the reason for many cases of poisoning in the sixties, seventies and even the eighties.[17,23,93,96,97] Their entry into chicken feed has repeatedly caused much damage to the broiler industry.[123] Poisoning of people and extended contamination of various objects by xenobiotics (III) and (IV) has been observed many times in the non-industrial sphere as well, for example in the inadvertent utilisation of effluent from chloro-compound manufacture,[66,67,70,71] in poisoning at electric power plants, where much polychlorovinyl insulation material is concentrated or there are transformers (capacitors) packed with PCB.[47,88,124,125]

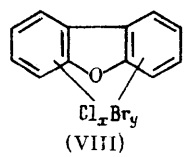
It has been established recently that polybromo-[126–129] and mixed polybromochloro-containing[130,131] dibenzo-*p*-dioxins and dibenzofurans of structure (V)–(VIII) are not less but in some cases more dangerous than the polychlorinated derivatives (III) and (IV). These are formed as byproducts in the manufacture of organic halides, on burning fuel in the presence of bromine compounds and also on processing or the destruction of industrial and domestic refuse.


(V)


(VI)

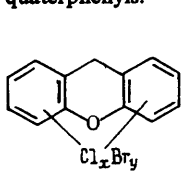
$n = x + y = 1$ to 8

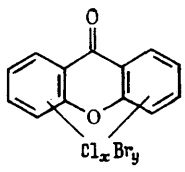

(VII)

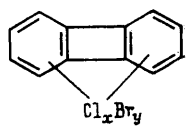

(VIII)

$n = 1$ to 8

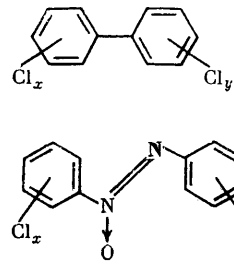
Many other organohalogen compounds possess the biological activity characteristic of dioxin (I). These include certain tricyclic compounds such as polychloro-, polybromo- or polychlorobromo-containing xanthenes (IX), xanthones (X) and biphenylenes (XI)[55,132,133] and also the structurally more complex polychlorinated quaterphenyls.[95,96,134]


(IX)


(X)


(XI)

Finally a series of bicyclic compounds such as polychlorobiphenyls,[95,96] polychloroazo- and polychloroazoxybenzenes[135] should also be included.

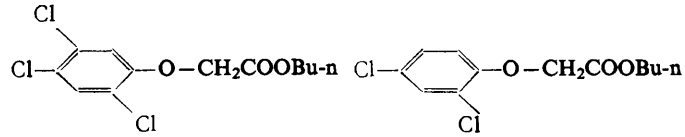


Many of the tri- and bicyclic compounds indicated accompany chemical production and are precursors of xenobiotics (III) and (IV) in nature.

In the industrially developed nations the attention of investigators was drawn long ago to the danger of permanent contamination of the biosphere with dioxin and related xenobiotics. This is evidenced by the appearance of numerous monographs, symposia, scientific conference proceedings,[1–43] reviews[44–114] and dissertations[136–145] devoted to individual aspects and to this problem as a whole. Since 1980 international cooperation has been effected within the framework of annual international scientific conferences devoted to the dioxin problem.[25–34] In several countries the problems linked with dioxins occupy one of the most important places in state ecological and ecologo-economic programmes.

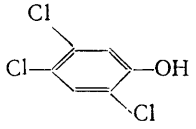
In the last two decades the problems of contaminating the biosphere with dioxins have been widely discussed by the public, in political circles and in the press. This was made possible by the active exposure of the material from two massive events in the years 1960–1970.

One of these was the war of the *USA in Vietnam* in which ~57,000 tons of the herbicide 'Agent Orange' containing (according to official data) about 170 kg dioxin (I) was applied to the territory of South Vietnam during 1962–1970.[35–41,72] The numerous communications generated on the massive disease of the population of this region and the participants of the war,[39,50,66,72,146–149] the negative effects of the herbicide on the child-bearing function of the women, its teratogenic action[146,147] and the more remote consequences of the disease[11,18,24] could not fail to cause alarm since the components of herbicide 'Agent Orange' [a mixture of the butyl ester of 2,4,5-trichlorophenoxyacetic acid, 2,4,5-T (XII), containing (I) as a contaminant, and the butyl ester of 2,4-dichlorophenoxyacetic acid (XIII)] were widely used in agriculture.


(XII) (XIII)

The other occurrence proved to be an *industrial incident* happening in July 1976 *in Seveso* (Italy).[67,69,99,100,106,150–156] At the ICMESA works the discharge took place, as a result of an accident,

of hundreds of tons of 2,4,5-trichlorophenol (XIV) which was accompanied by the discharge of dioxin (I) and other xenobiotics of the type of (III) and (IV).



(XIV)

No less than 500 people suffered drastically from contamination by the noxious cloud in the neighbouring territory. Several thousand residents of neighbouring small villages were subjected to the action of dioxin, thousands of domestic animals perished. It was considered that from 2 to 3 kg, according to some assessments up to 5 kg, dioxin was dispersed as a result of the accident. It is difficult to know the amount more precisely since the procedures of the seventies did not permit complete recovery of dioxin from the samples analysed.[154]

Both these occurrences and also cases, less known to the wider public, of contamination of land such as in the state of Missouri (USA),[66,67,70,71,157,158] revealed the horrible perspective of remote consequences of global contamination of the biosphere by xenobiotics of the dioxin type. This could not fail to exert psychological pressure on mankind and led to increased attention to dioxin as the source of possible global ecological disaster, in principle more serious and immeasurably more dangerous than the multiton discharge of other contaminants.

The analytical chemical aspects of the problem of dioxin and related compounds are considered briefly (chiefly from foreign published material) in the present review. Problems of the physicochemical and medico-ecological characteristics of dioxins, some technological problems, etc. are also considered in part. Attention is mainly paid in the present review to the contaminants which are most widespread in nature, viz. chlorinated dibenzo-*p*-dioxin (III) and dibenzofuran (IV), from the sum total of xenobiotics (III)–(XI) and the corresponding bicyclic compounds.

II. Physicochemical properties of dioxin-type xenobiotics

Resolution of the practical problems of the organic analysis of xenobiotics (III)–(VIII) is complicated appreciably by the problem of their *isomer composition*. Thus the archetype of all the substances, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (I), is only one of the 22 possible isomeric tetrachlorodibenzo-*p*-dioxins. Equally 2,3,7,8-tetrachlorodibenzofuran (II) is only one of the 38 possible isomeric tetrachlorodibenzofurans. Altogether the total of uniformly substituted polychloro- or polybromodibenzo-*p*-dioxins and dibenzofurans comprises 420 individual substances. The isomer composition of mixed chlorobromo-containing xenobiotics (VII) and (VIII) is even more abundant.

Data on the complete isomeric composition of xenobiotics (III)–(VIII) are correlated in Table 1.[130] To complete the picture, data on compounds (IX)–(XI) are also included although the xanthenes and xanthones at present are not important for natural processes and the biphenylenes are converted into compounds (III) and (IV). As was shown in the last decade, practically all of the 5020 substances of classes (III)–(VIII) may form part of microdischarges of modern technology. Only tetra- to octa-substituted (III)–(VIII) containing halogen atoms in positions 2,3,7,8 are highly dangerous to man and nature. There is obviously an order of difficulty in the analytical chemistry connected with the need to identify and estimate the tens or hundreds of xenobiotics most dangerous to the environment among thousands of similar substances.

Table 1. Number of homologues and isomers in families of tricyclic halogen-containing xenobiotics (III)–(VIII) and in compounds (IX)–(XI) as a function of the number of chlorine and/or bromine atoms in the molecule.

$n=x+y$	Number of isomers								
	(III)	(IV)	(V)	(VI)	(VII)	(VIII)	(IX)	(X)	(XI)
1	2	4	2	4	0	0	8	8	4
2	10	16	10	16	14	28	60	60	34
3	14	28	14	28	84	168	224	224	112
4	22	38	22	38	254	496	572	572	298
5	14	28	14	28	420	840	896	896	448
6	10	16	10	16	452	880	912	912	472
7	2	4	2	4	252	504	512	512	256
8	1	1	1	1	74	134	136	136	76
Total	75	135	75	135	1550	3050	3320	3320	1700

Further complexity in the organisation of analysis may be explained by the presence in microdischarges from existing technology of functionally substituted xenobiotics (III)–(VIII) containing NO_2, NH_2, Alk and other groups in place of halogen. These are highly dangerous substances in several cases. Among them, and among (III)–(VIII), competitive antagonists of the highly toxic xenobiotics are encountered which reduce the effect of the latter.[132,159–161] This may also lead to an increase in the volume of analytical work and in its complexity as a result of a wider background and limitations on the use of biological methods of analysis.

Difficulties arising in connection with the broad isomeric composition of xenobiotics (III)–(VIII) are also caused by inadequate measurements of physical and chemical properties in series of regioisomers. The physical properties of the xenobiotics are determined mainly by their overall chemical nature, including the number of halogen atoms in the molecule, and the chemical properties also depend essentially on the positions of halogen atoms. Correspondingly regioisomers differ appreciably in biological activity and in their rate and route of metabolism in nature. Both bioactivation and biodegradation of compounds (III)–(VIII) are possible in nature.[162–164] Thus xenobiotics (III)–(VIII) constitute a system of contamination of nature which is not only complex but also changing constantly in direction and time.

Three groups of properties are particularly important for practical analytical chemistry. First there are properties determining the limiting content of xenobiotics in various phases (water, soil and air),

then properties governing the form of their existence and behaviour in these phases and finally properties controlling the behaviour of xenobiotics at phase boundaries (air–water, soil–water, water–octanol, phase–living organism).[44,45,73–75,165–195] Certain physicochemical characteristics of compounds of the (III) family, derived from published data,[45] are correlated in Table 2. These also permit opinions to be formed on the properties of xenobiotics (IV)–(VIII) [some properties of compounds (IV) are given[141]]. It follows from the data presented that such key properties of xenobiotics (III) as solubility in water, distribution coefficient in the octanol–water system (K_{OW}) and vapour pressure (P^S) do not change regularly with increasing number of chlorine atoms in the molecule.

Characteristically dioxin (I) and also the corresponding furan (II) are crystalline substances with melting points 305[45,49,196] and 227–228 °C[141] respectively. The other tetrachloro derivatives (III) and (IV) are also high melting. A lower melting point is characteristic for the less chlorinated compounds (III) and (IV).[45,141]

The good solubility of various (III) derivatives in organic solvents is determined by the *lipophilic* (hydrophobic) nature of these nonionic organohalogen compounds. In particular the solubility of dioxin (I) is (in g litre^{-1}) 0.57 in benzene, 0.37 in chloroform, 0.11 in acetone and 0.05 in octanol.[196] At the same time these xenobiotics are practically insoluble in water (2.10^{-7} g litre^{-1}).[196] It must however be stressed that, as recent measurements have shown, under practical conditions the solubility of dioxin (I) in water may be both less[169] and significantly greater[170] than that measured initially in double distilled water.[196] This is explained by the high capability of (I) towards complex formation with water-soluble polymers.[183] These latter substances, such as humic and fulvic acids, are absent from super-pure water,[170] however they are present under actual conditions of analysis. Derivatives of the (IV) series are just as poorly soluble in water as those of the (III) series.[197]

The *volatility* of the xenobiotics under consideration is usually insignificant.[45] For example the vapour pressure of dioxin (I) under ideal conditions is 1.7×10^{-6} mm Hg.[49,196] However even in 1973 it was reported that (I) may actually be present in air at a 'supersaturated' concentration,[198] which is caused by its effective adsorption on various aerosol particles.

It follows from these data that the actual concentrations of (I) determined by analysis in two most important phases, viz. air and water, may prove to be greater than the concentration determined by the physicochemical characteristics, volatility and solubility, obtained under ideal conditions. In addition the transport of xenobiotics in these media is not subject to such an extent to the rules of gas dynamics or true solutions. How much is determined by the behaviour of their carriers, aerosol particles in the air and molecular complexes in soil and water?

Two other physicochemical characteristics of the xenobiotics under consideration are analytically and toxicokinetically important. These are the *high adhesive ability* in relation to different types of evolved surface, including soil, ashes, residues, etc.[166,199,200] (this property depends appreciably on the presence of other organic substances in the material[166,179]) and the *high distribution coefficient in the octanol–water system* (Table 2).[178] In reality these two properties determine the special behaviour of xenobiotics in the environment and their entry into living matter.

It is known for example that in inanimate nature xenobiotics (III) and (IV) gradually transfer into the organic phase of soil or water migrating onwards as complexes with organic substances (they pass into the air, reservoirs, and are incorporated into food chains).[165–181] Having entered into living organisms xenobiotics accumulate in them (bioconcentration).[182–195] It has been proposed that the coefficient of *bioconcentration* (BCC) is linked with the distribution coefficient in the octanol–water system by a simple relationship[184,185] (value of BCC are given in Table 2 and were calculated with the aid of the

Table 2. Some physicochemical characteristics of polychlorobenzo-*p*-dioxins (III).

Compound	Mp, °C	Water solubility, ng litre^{-1}	lg K_{OW}	Vapour pressure P_L^S, Pa	Henry constant, Pa m^3 mol^{-1}	Molar volume, cm^3 mol^{-1}	Predicted log BCC
2-Cl-DD	105.5	278 000 (25° C)	4.94	$8.58 \cdot 10^{-2}$	14.82	212.9	3.52
2,3-Cl_2-DD	164.0	14 900 (25° C)	4.70	$9.26 \cdot 10^{-3}$	6.61	233.8	3.34
2,8-Cl_2-DD	151.0	16 700 (25° C)	4.70	$2.47 \cdot 10^{-3}$	2.13	233.8	3.34
1,2,4-Cl_3-DD	129.0	8 410 (25° C)	6.45	$1.07 \cdot 10^{-3}$	3.84	254.7	4.67
2,3,7,8-Cl_4-DD	305.0	19.3 (22° C)	7.02	$5.79 \cdot 10^{-5}$	3.34	275.6	4.82
1,2,3,6-Cl_4-DD	219.0	320 (20° C)	7.13	$5.81 \cdot 10^{-5}$	0.71	275.6	5.19
1,2,3,4,7-Cl_5-DD	196.0	118 (20° C)	7.44	$4.31 \cdot 10^{-6}$	0.264	296.5	5.42
1,2,3,4,7,8-Cl_6-DD	273.0	4.42 (20° C)	7.79	$1.45 \cdot 10^{-6}$	4.52	317.4	5.69
1,2,3,4,6,7,8-Cl_7-DD	265.0	2.4 (20° C)	8.20	$1.77 \cdot 10^{-7}$	0.133	338.3	6.00
Cl_8-DD	332.0	0.4 (20° C)	8.60	$1.19 \cdot 10^{-7}$	0.683	359.2	6.31

proposed expression log BCC = 0.76 K_{OW} − 0.23[185]). However, the experimental values of BCC for xenobiotics (III) and (IV) in animals or in plants (for example in fish values of BCC vary from 2000 to 6000[188]) proved to be significantly lower than might have been expected[165] proceeding from data on the distribution coefficients of xenobiotics in the octanol–water system and on their water solubility. This is explained by the substantial influence of the biochemical special features of the accumulating organisms on the degree of absorption and the retaining ability for xenobiotics and also on the substantial difference of the properties of pure xenobiotics from the properties of their actual adducts with organic substances taking part in biotransfer.[181–183,186]

One of the analytically important characteristics of compounds (III) and (IV) is their extreme *chemical stability* in acid and alkaline solutions and also their stability towards oxidation under uncatalysed conditions.[201] This determines the high stability of xenobiotics (III) and (IV) in the environment. In particular the *half-decomposition time* of dioxin (I) in soil exceeds 8–10 years.[100,156,202]† The roles of photolysis on the surface[204] and of biodegradation[205] in their breakdown are insignificant. However it is necessary to consider the ability of highly chlorinated compounds (III) and (IV) with n = 7 and 8 to be converted photolytically on a soil surface into dioxin (I) and other xenobiotics with a lateral 2,3,7,8 disposition of chlorine atoms.[206] Their ability towards hydrolysis and nucleophilic substitution in strongly alkaline alcoholic solutions on heating is also known and may seriously distort analytical data.[207]

The irreversible thermal breakdown of organochlorine xenobiotics considered above occurs at temperatures somewhat exceeding 750 °C.[208] It was shown subsequently[209] that the thermal decomposition of xenobiotics (III) and (IV) is a reversible process at temperatures up to 1200 °C. Only maintaining the xenobiotics for 4–7 sec at a temperature of 1200 °C and above led to irreversible fragmentation. This circumstance produces specific requirements for the mode of operating incinerators (INC).[65] The organobromine xenobiotics (V) and (VI) are also thermally stable. Their formation and not their destruction occurs more effectively at 800 °C.[210] At the same time organochlorine xenobiotics and their organobromine analogues are comparatively readily decomposed in actual solution by UV irradiation.[211–214] Other means of non-thermal decomposition of xenobiotics are known.[211]

At the present time many of the 210 organochlorine compounds of the (III) and (IV) types of xenobiotics have been synthesised, isolated pure and studied.[198,215–220] The *danger* of such work for personnel has been reported[118] as has the need to observe the most strict precautions when working with these substances.[219] Recently there have been reports of the synthesis and investigation of a series of organobromine compounds of the (V) and (VI) type,[126–129,221] of mixed organochlorobromo compounds of the (VII) and (VIII) types,[126,127,130,131] and also of organohalo-xanthenes, xanthones and biphenyls (IX)–(XI).[132,222] The synthesis of analytically important compounds enriched with particular isotopes has been carried out.[223,224]

The *physicochemical investigation* of xenobiotics (III) and (IV) is accompanied by significant difficulties caused both by the diversity of their homology and isomeric composition and by the high toxicity of many of them. None the less fairly similar chromatographic and mass spectrometric data have been obtained for many individual isomers which is particularly important when organising their practical determination in various objects.[217–219,225–227] Spectroscopic investigations of these compounds have also been carried out in radiofrequency[216,218,220,228–231] and optical[215,232,233] ranges.

^{1}H NMR spectra have been described for many isomers of (III) and (IV)[218,220,228–230] and ^{13}C NMR spectra of certain isomers,[216] ^{1}H and ^{13}C relaxation times have been measured for individual isomers.[230,231] The possibility has been noted of using ^{1}H NMR spectroscopy in the identification and determination of individual isomers of (III) and (IV) in mixtures of them at the microgram level.[228–230] It must be stressed that ^{13}C NMR spectroscopy is an uncommon physical method of investigation, which allows spectra of previously unstudied substances to be predicted using already investigated substances as examples. A successful example of such type has been demonstrated[234] in which calculation of the ^{13}C NMR spectra was carried out for 69 isomers of the (III) series, including all those highly toxic, on the basis of known spectral data on 6 nontoxic isomers.[216]

When determining the *spatial structure* of dioxins (III) by diffraction methods it was found that the 1,2,3,7,8,9-hexachlorodibenzo-*p*-dioxin molecule (the source of the known epidemic in the broiler industry of the USA[123]) is non-planar (the angle between the two faces about the O–O axis is 4.8°).[235] The structure of 2,8-dichlorodibenzo-*p*-dioxin was analogous but the molecules of 2,7-dichloro-, 2,3,7,8-tetrachloro- and octachlorodibenzo-*p*-dioxin proved to be practically planar.[236] It should be mentioned that the actual planarity of the molecule (together with the lateral disposition of the halogen atoms in the aromatic rings) is one of the key properties determining the high toxicity of xenobiotics (III) and (IV).[237] It is also interesting that in the compound (III) series the C–Cl bond length is progressively reduced with an increase in the number of chlorine atoms in the molecule.[236]

III. Sources

The known data on the sources and routes of formation of xenobiotics (III)–(VIII) have been published in a series of reviews.[48,56,58,59,61,238] Several mechanisms have been considered for the generation of these xenobiotics in relation to structure, properties of precursors and conditions of conversion. These may be nucleophilic substitution reactions, radical processes and pyrolysis. In addition an increase in the number of halogen atoms in preformed tricylic compounds occurs by electrophilic substitution of hydrogen by halogen.[58]

Sources of the xenobiotics under consideration have an exclusively *technogenic character*[239,240] although attempts are known to explain their appearance in the biosphere by forest and steppe fires.[241] The appearance of the xenobiotics in the environment beginning in the

† The half-decomposition time of dioxin (I) in soil has been reliably established for many years.[23,50] An outside report appeared more recently indicating it was from 0.5 to 1 year.[203] In the USA a similar sort of error had far reaching consequences. After inadvertent contamination of many parts of the state of Missouri in 1971–1972 by effluent from hexachlorophene manufacture containing significant admixture of dioxin (I) and the disclosure of this happening in 1974, decontamination of the territory was not carried out for many years in the hope of natural decomposition of dioxin in the soil. Only at the beginning of the eighties when it was revealed that the half-decomposition time of (I) was not 0.5 to 1 year but approximately 10 years did massive operations begin on the destruction of the consequences of the accident, including destroying the dioxin in dumps. This proved to be even more difficult to accomplish and incomparably more expensive.[67,70,71]

1940's was caused by the development of various technologies linked chiefly with the manufacture and use of organochlorine compounds. In any case proof has not been found of the accumulation of these xenobiotics in bottom sediments of rivers and lakes formed prior to 1940, i.e. before the beginning of manufacture of herbicides based on chlorophenoxyacetic acids.[239] The sources of xenobiotics (III)–(VIII) are subdivided according to economic-territorial criteria into local and diffuse (spatially distributed) and, according to the rate of accumulation in the environment and in living matter, into continuous or periodic.

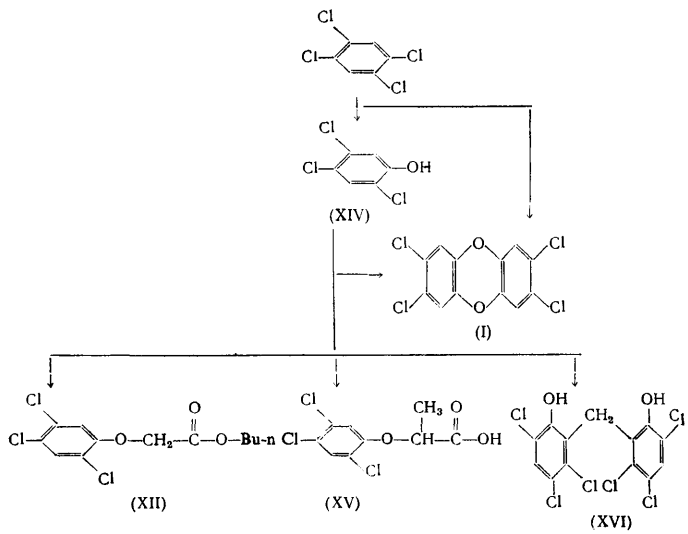
Sources delivering xenobiotics (III)–(VIII) into the environment are divided chiefly into three groups.[63,238]

1) The operation of defective manufacturing technology and the application of chemical production (of aromatic and aliphatic organochlorine and -bromine compounds, inorganic chlorides, any chemical products with the intermediate use of chlorine, inorganic chlorides, organochlorine and -bromine compounds, including use as catalysts and solvents), which are characterised by a) the presence of waste water and effluent of such manufacture,[242] b) premeditated introduction into nature of chemical products containing admixture of xenobiotics or their precursors and c) imperfect safety measures when burying or recovering effluent of chemical manufacture containing admixture of (III)–(IV).

2) Discharges from undertakings of any type (cellulose-paper, metallurgical, etc. and also undertakings specialising in the combustion of industrial and domestic refuse).

3) Automobile exhausts.

The most toxic xenobiotic (I) is formed in the manufacture of the phenoxy herbicides 2,4,5-T (XII) and Silvex 2,4,5-TP (XV), which are widely used in agriculture, and also of the antibacterial preparation hexachlorophene (XVI). Dioxin (I) arises as a side product under the actual conditions of manufacture of 2,4,5-trichlorophenol (XIV) which is the precursor of compounds (XII), (XV) and (XVI) [for example when the process is conducted at a temperature exceeding that (180°) required by the technological regulations[8,79,124]].



The content of dioxin (I) in 2,4,5-trichlorophenol (XIV) may reach 6.2 p.p.m depending on the special features of the technology‡.[243] In such final products as herbicides (XII) and (XV), the content of (I) proved to be subtantially greater [prior to 1970 the amount of (I) in products (XII) and (XV) reached 30 and even 100 p.p.m., later it was reduced to 0.01 p.p.m.[8,68]]. Considering that the greatest volume of production of 2,4,5-T occurred in 1960–1970 (its output during this period was 48.6 thousand tons) this means that the maximum quantity of dioxin (I) which was manufactured during this time may have reached 4800 kg. Significant quantities of hexa-, hepta- and octachlorodibenzo-*p*-dioxins (up to 1000 p.p.m.) have been detected in tri- and tetrachlorophenols[243] and in pentachlorophenol, widely used as a wood preservative.[243,244] In particular in the USA, the largest manufacturer of pentachlorophenol, several tons of xenobiotics (III) and (IV) were in fact 'discharged' in 1972–1977.[68]

Xenobiotics (III) and (IV) are formed in significant amounts in the *cellulose–paper industry* at the stage of bleaching the pulp with chlorine and compounds containing it.[56,133,144,245–251] This source of contamination of the environment with xenobiotics (III) and (IV) was first considered even in 1974.[245] However only investigations of recent years showed that xenobiotics are present not only in finished timber products[250] and in paper (at the p.p.t. level),[247] but also in all the technological chain, viz. the pulp itself, filtrate, the filtered off mass,[248–250] and in the solid and liquid effluent (up to 400 p.p.t.)[133,249] and the gases discharged from combustion. Up to 22 different isomers of (III) and (IV) were detected in the waste products from the cellulose–paper industry. These had 4 to 8 chlorine atoms and included 12 which are particularly toxic. The most toxic dioxin (I) was present in these mixtures in appreciable amounts.[248] Increased concentrations of xenobiotics (III) and (IV) were also found in fish, crabs and other representatives of aquafauna, inhabiting the vicinity of the drains of these undertakings.[133,249]

Incinerators (INC), which are widely used in industrially developed nations for the destruction of domestic and nontoxic industrial waste, and equipment for the destruction of toxic waste and effluent, are a steady source of xenobiotics (III) and (IV) and related substances. The first INC for the destruction of domestic waste was built in England in 1876 and at present such equipment operates for various purposes, including energy production, in great numbers in Western Europe, North America and Japan. The volumes of waste destroyed are very large. Japan burns 50 million tons waste in a year, the USA 28 million (7% total volume), FRG 8 million, Sweden 7 million, etc. Only in Canada is relatively little waste burned, viz. 1–2 million tons (in comparison it is reported that in Paris alone up to 3 million tons is burned in a year).[22]

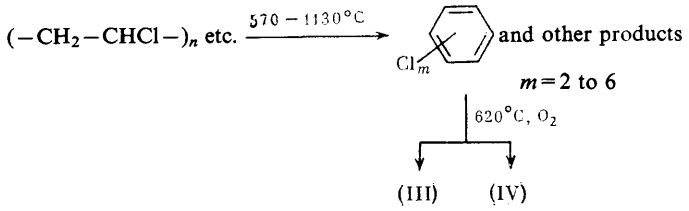
Microadmixture of (III) was found in 1977 for the first time in light ashes and effluent gases from INC in the Netherlands.[252] Later an analogous admixture was detected and studied in discharges from INC in other industrially developed countries, viz. USA and Canada,[52,253–257] England,[258,259] Switzerland and Sweden,[260–264] Italy,[265–268] FRG,[269–271] France,[272] Belgium,[273] Japan,[274–279] Austria,[279] Denmark,[280,281] Norway[282] and other countries.[51,283,284]

One INC of average productive capacity (50–200 thousand tons per year) emits 1–100 ng m^{-3} or 1–100 g xenobiotics (III) and (IV)

‡ Here and subsequently the units of measurement used will be those taken in analytical chemistry for trace amounts of organic substances, viz. p.p.m. (μg g^{-1}, mg kg^{-1}), p.p.b. (ng g^{-1}, μg kg^{-1}), p.p.t (pg g^{-1}, ng kg^{-1}), p.p.q (fg g^{-1}, pg kg^{-1}).

per year in comparable concentrations.[56,142] The amount of xenobiotics formed on burning depends on the mode of burning and the character of the refuse being destroyed. However on the whole none of the existing technologies for burning refuse is capable of preventing their formation.[48,51,63,239–240,274] Installations for destroying industrial refuse do not differ from INC in this respect.[261] Usually the attention of investigators is centred on xenobiotics passing out with effluent gases and light ash, however their presence in furnace scale transferred to burial is no less dangerous. Scales are highly toxic discharges as a result of their high xenobiotic content and their accumulation in small sized dumps.[274]

Xenobiotics (III) and (IV) are formed in particularly large amounts when burning waste containing compounds, such as polyvinyl chloride, which contain halogen atoms.[246,259,261]



Burning of bromine-containing contaminants, which are associated with many textile and other materials in amounts up to 10–20% as fire-repellants,[285] is accompanied by the formation of organobromine xenobiotics (V) and (VI).[128,129,210,286] Mixed organochlorine-organobromine compounds (VII) and (VIII) have been detected in discharges from INC.[287,288]

Routes for the accumulation of xenobiotics (III)–(VIII) have still not been finally clarified.[58,246,289] It was considered[51,246] that they are formed when processing refuse or remained undestroyed in the process for burning refuse containing these xenobiotics in trace amounts. For example representatives of these xenobiotics, chlorophenols, have been obtained on combustion of other organic materials in the presence of inorganic chlorine compounds. At the present time one is persuaded that xenobiotics (III)–(VIII) are formed in all high temperature processes involving carbon and any chlorine compound in any valency state,[270,290] but catalysts are always found in such complex heterogeneous systems. Both metallic surfaces and the surface of light ash have proved to act in this way.[289]

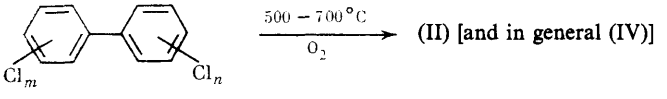
A new group of local sources has recently been revealed.[261] As it turned out xenobiotics (III) and (IV) are formed in *metallurgical plants* such as the electrochemical preparation of nickel and magnesium oxides,[291] in steel casting manufacture,[292] on smelting iron and copper scrap,[261] etc. Xenobiotics (III) and (IV) were everywhere, in waste water and discharges from these works, in the surrounding soil, in air tanks, etc.

Domestic stoves operating on coal and oil may also be local sources of the xenobiotics under consideration. The low content of (III) and (IV) in flue gases may not cause alarm[261] due to the low probability of the appearance of halogen sources in the fuel.[63] However recent data[293] showed that it is impossible to disregard this source, particularly due to its widespread distribution and uncontrolled nature.

The polychlorinated (PCB) and polybrominated biphenyls (PBB) are dangerous sources of xenobiotics of the type of (IV) and (VI). Thanks to their electrical and thermal characteristics, incombustibility and high chemical stability, these substances are widely used as liquid dielectrics and high temperature heat-transfer agents. Their worldwide manufacture exceeds 4 million tons per year.[55] Xenobiotics (IV) and (VI) are formed in the synthesis of PCB and PBB.[122,134,294] The content of (IV) in some PCB reaches 33 p.p.m.[295]

In addition xenobiotics (IV) and (VI) are also formed on overheating and burning PCB[296] and PBB.[128,137] Thus the content of compounds (IV) in rice oil contaminated with PBB proved to be two orders of magnitude greater after using it for food than in the initial PCB.[297] In conflagrations at transformer stations the concentrations of (IV) and related xenobiotics may prove to be so significant[48,59,295,298] that the restoration of damaged buildings becomes impossible.[125] In particular 8 fires in transformers containing PCB were recorded in the USA in 1981–1985 alone, including a fire at the White House in 1985. About 20 explosions and fires at capacitor installations containing PCB were known in Western European countries.[296]

The process of thermal formation of xenobiotics of the (IV) type is represented in general in the following manner.[137]



Several more detailed mechanisms of this reaction have been proposed which explain the isomeric composition of xenobiotics (IV) formed on combustion of PCB.[59]

The *exhaust gases of motor vehicles* may serve as an example of a diffuse source of xenobiotics (III)–(VI) and was described even in 1980.[241] An increase in the octane number of petrol is usually achieved by introducing dichloro- or dibromoethane or other organobromine substances together with $(C_2H_5)_4Pb$ or $(CH_3)_4Pb$. The former are precursors of harmful substances,[299] including xenobiotics (III)–(VIII).[300–303] The average output of xenobiotics by a motor vehicle using ethylated petrol is 30–540 pg km^{-1} (in dioxin equivalents, see below).[301] These amounts may be considered insignificant at first glance. The locations of heavy contamination by dioxins of motorways and regions adjacent to them are the fault of motor transport. These include poorly ventilated roadway tunnels,[142,304] soil alongside motorways with busy traffic, etc. It is also impossible to ignore the detection of xenobiotics in the exhausts of motor vehicles operating on unethylated petrol.[238]

The *water supply system* may prove to be a diffuse source of (III) and (IV). There were no communications for a long time on the detection of serious quantities of xenobiotics in drinking water after its chlorination, although the formation of (III) and (IV) in significant amounts is inevitable after introducing phenolic substances into chlorinated water after their discharge from industrial undertakings. Events which occurred in spring 1990 in Ufa, when chlorination of the water supply was obliged to be stopped due to the introduction of phenols into it by the Khimprom Industrial Combine, is direct confirmation of this.[305] It is possible

that in this case there was a direct dropping of dioxins (III) into the river and they then entered the water intake (*Arguments and Facts*, 1990, No. 33).

Industrial and other *waste products* eliminated from operations by their simple burial, storage or use may also prove to be dangerous. Such happenings were noted in Japan in places for the accumulation of large quantities of ash from INC containing (I) and (II) at 6.7 and 1.3 p.p.b. respectively.[274] Another example is the utilisation of output from PCB operations. In Japan for example after prohibition of PCB use residues (5000 tons) were burned[23] and led to the discharge of (IV). In the USA transformers and capacitors containing 600 thousand tons PCB derivatives scrapped in 1929–1977 were stored in dumps. The presence in them of only 1 p.p.b. xenobiotics implies the accumulation in the dumps of 0.6 kg dibenzofuran (II).[306] However it is known that the actual content of (IV) in PCB is significantly greater and reaches 33 p.p.m.[295]

Just how serious a problem is the storage of waste products from the manufacture of organochlorine pesticides may be judged from data of the USA,[61,307–310] FRG[311] and the Netherlands.[312–314] The quantity of dioxin (I) contained in waste products from 2,4,5-trichlorophenol (XIV) manufacture in dumps in New York state (USA) in the vicinity of Canada has been estimated at 45 kg.[61,307] In FRG in areas near Hamburg segregated for the storage of waste products from the manufacture of the herbicides 2,4,5-T (XII), Silvex (XV), lindane, etc., huge amounts (at the level of p.p.m.) of both dioxin (I) itself and many other xenobiotics (III) and (IV) were found in soil.[311] Close to Amsterdam 2000 tons organochlorine waste products, mainly from the manufacture of the herbicides 2,4,5-T and lindane, had been stored in steel drums during 1955–1970. By the beginning of the eighties the majority of the drums had disintegrated [at that time the actual waste products still contained large amounts of dioxin (I) (up to 21 p.p.m.) and (IV) isomers] and the contamination of soil layers close to the dump by dioxin (I) reached 8 p.p.b.[312,313]

The reason for the contamination of land in Missouri (USA) in 1971–1972 was the unjustified use of waste products of hexachlorophene (XVI) manufacture, which contained a large amount of dioxin (I) in vat residues. As a result in more than 40 populated localities, 5000 inhabitants proved to have been dusted with ~29 kg dioxin (from 22 to 68 kg according to different assessments). In 1974 when dioxin (I) was identified its concentration in soil in individual places reached 30 p.p.m. and even in 1983 when examination of the health of all the inhabitants living in the contaminated territory began localities were found with a contamination of up to 2.2 p.p.m.[70]

Finally the industrial manufacture of dioxin-containing herbicides itself may be converted from a local source to a diffuse source since the transportation of herbicides by the commercial route and then their spraying over agricultural or other land is practically uncontrollable. Thus the reserves of herbicides (XII) and (XV) accumulated in the USA, particularly abundant in dioxin (I), have entered many countries of the world, especially after the prohibition of their use in the USA in 1979. Several states have 'imported' dioxins from the industrially developed countries as contaminants in the herbicide 2,4-D (XIII). Although the content of the most toxic dioxin (I) in them is not large admixture of other mono-, di-, tri- and tetrachlorodibenzodioxins (III) is fairly considerable.[243]

As a consequence a huge amount of dioxin (I) and other substituted dioxins is circulating in the biosphere at present, and has been introduced over several decades together with numerous organochlorine herbicides. The herbicide 'Agent Orange' for military purposes is one of them. The average content of (I) in the latter is officially considered to be close to 2 p.p.m.§ and in previous samples (obtained from non-toxic isomers of hexachloran) it reached 47 p.p.m.[17] Overall, pesticides based on 2,4,5-trichlorophenol (XIV) are *one of the main sources of contamination of nature by dioxin (I)* and also by other less toxic but not less dangerous xenobiotics of the (III) and (IV) types.[214,315] In this context it is difficult to agree with the statement that 'the fraction of pesticides and other products of the chemical industry in the contamination of the environment is less than 5%.[64] This opinion does not rest on facts if the actual influence on the biosphere and not the volume of refuse discharged is considered.

In the middle of the eighties a first attempt was made by scientists of FRG, the Netherlands and USA at a *comparative analysis of the importance* for the active life of the biosphere of *various sources of xenobiotics* (III) and (IV).[68] This is a particularly complex problem since the known sources have differences in principle in quantitative and qualitative respects. As it turned out the considered sources may be arranged in decreasing order of danger as follows:

- manufacture and use of the herbicide 2,4,5-T (XII),
- pentachlorophenol,
- tetrachlorophenol,
- 2,4,5-trichlorophenol (XIV),
- polychlorodibenzofurans (IV) and PCB,
- destruction of domestic refuse in INC,
- fires in transformer installations containing PCB,
- operations of chloro-compound manufacture,
- combustion of chemical waste.

In conclusion it is emphasised that the available data on sources of xenobiotics (III)–(VIII) reveals only some of the most dangerous contaminated objects (or regions) with the aim of their analytical inspection for dioxin content. In future a large number of technologies will have to be studied from the point of view of the danger of generating dioxins. These will include the thermal reprocessing of carbon compounds in the presence of inorganic chlorine compounds, mild processes for the interaction of biomaterials with chlorine-containing oxidising agents, and also biotransformations of (III)–(VIII) from various products of organohalogen synthesis.

IV. Toxicity, medical effects and their consequences

After the discovery of the high acute toxicity of organochlorine xenobiotics (III) and (IV)[2–18,24,80,81,119,316] and their bromine-containing analogues (V) and (VI)[76,317] a large number of papers appeared devoted to the study of the toxicological features of these substances.[76–87,119,141,316–325] Data on the acute toxicity of

§ However some authors do not agree with the official point of view and suggest that the content of (I) in the military mixture of 'Agent Orange' was 5000 times greater than in herbicides used in agriculture. Turning in passing to the problem of the toxicity of the 'Agent Orange' mixture, which became widely known after the war in Vietnam, it should be mentioned that the presence in it of the highly toxic dioxin (I) became known to the scientific USA in 1963 and to the Presidential Scientific Consultative Committee in 1965. In 1970 the corresponding hearing took place in the US Congress after which use of the military mixture ceased.[23,148]

xenobiotics (III)–(VI) were obtained in animals and their chronic action has been studied both in animals and in man (including volunteers).[79]

Dioxin (I) possesses the maximal toxicity.[316] It is more toxic than cyanides, strychnine and curare.[326] Its toxicity is greater than, or at least comparable with, the toxicity of the antichlolinesterase poisons tabun, sarin, soman and VX gas.[326,327]

There is confirmation[91] that dioxin (I), the most toxic of substances synthesised by man, cannot in principle be regarded as a journalistic exaggeration. Dioxin is accepted as a standard for the toxicological assessment of all the xenobiotics of the (III)–(VIII) types. It must however be emphasised that the main danger of dioxin (I) and xenobiotics (III)–(VIII) in general resides in their cumulative action and the delayed consequences of chronic poisoning by extremely small doses.[49,86,93]

Table 3. Acute toxicity of some xenobiotics (III)–(VI), insecticides and toxic substances.[81,319,327–329]

Compound	LD_{50}, μg kg^{-1} (ppb)			
	guinea pig	monkey	mouse	rat
Xenobiotics (III)				
2,8-Cl_2-DD	>300 000		8 470 000	>5 000 000
2,3,7-Cl_3-DD	29 444		>3 000	>1 000 000
1,3,6,8-Cl_4-DD	>15 000 000		>2 987 000	>10 000 000
2,3,7,8-Cl_4-DD (I)	0.6–2.0	<70	114–284	22–45
1,2,3,7,8-Cl_5-DD	3.1		337.5	
1,2,3,4,7,8-Cl_6-DD	72.5			825
1,2,3,6,7,8-Cl_6-DD	70–100		1250	250
1,2,3,4,6,7,8-Cl_7-DD	>600			
Cl_8-DD			>4 000 000	>1 000 000
Xenobiotics (IV)				
2,8-Cl_2-DF			>15 000 000	>15 000 000
2,4,8-Cl_3-DF			>15 000 000	>5 000 000
2,3,7,8-Cl_4-DF	5–10	<1000	6 000	1 000
2,3,4,7,8-Cl_5-DF	<10			
2,3,4,6,7,8-Cl_6-DF	120			
Xenobiotics (V)				
2,3,7,8-Br_4-DD				⩽1000
Xenobiotics (VI)				
2,3,7,8-Br_4-DF	<15			
Insecticides				
DDT			200 000	300 000
Toxic substances				
Tabun		208		
Sarin		83		
Soman		156		
VX		20.1		

Information on the *acute toxicity of xenobiotics* (III)–(VI) is given in Table 3. Apart from dioxin (I), 1,2,3,7,8-Cl_5-DD possesses high toxicity. Some chlorinated derivatives of the (IV) series, particularly (II) and two of its Cl_5-isomers, viz. 1,2,3,7,8-Cl_5-DF and 2,3,4,7,8-Cl_5-DF, are also close in toxicity.[319,321] The toxicity of the xenobiotics indicated is many orders of magnitude greater than the toxicity of DDT and, which is very important, depends significantly on the species peculiarities of the experimental animals. The toxicities of the organobromine derivatives (V) and (VI) [organobromine analogues of (I) and (II)] and also 2,3,7-Br_3-DD[76,317] and of the mixed organobromine-chlorine compounds (VII) and (VIII) are just as high.[322]

The remaining compounds of types (III) and (IV) are less toxic than (I) and (II) although not all representatives of the (III) and (IV) series and even fewer of (V)–(VIII) have been studied in such detail.[81] In compounds of the (III) and (IV) series the xenobiotics containing from 4 to 6 chlorine atoms are particularly toxic while the presence of a lateral 2,3,7,8-Cl_4 fragment is an obligatory condition for high toxicity. In the organochlorine series there are 12 such isomers [5 in the (III) family and 7 in the (IV) family] but there are 568 if bromine and mixed chlorine–bromine compounds are considered.[130] On increasing or decreasing the number of halogen atoms the toxicity of compounds is sharply reduced.[81,319] However the danger of xenobiotics (III) and (IV) for man and nature is not just their acute toxicity. Almost all polyhalogenated compounds containing the 2,3,7,8-Hal_4 fragment, including the penta- and octa-substituted derivatives, are dangerous by various tests.[77–82,319]

The toxicological special features of the xenobiotics under consideration are linked primarily with their high lipophilicity and exceptional stability in the environment and in living organisms.[330] The lipophilic nature of the xenobiotics enables their accumulation in the organic phase of the biosphere and bioconcentration in living organisms. The xenobiotics accumulate efficiently in representatives of fauna, mainly in lipid tissue (approximately 90%[331]), liver, thymus and the blood-producing organs[142,151,331–335] and are eliminated very slowly (but from man they are practically not eliminated).[77,336,337] *Bioconcentration* is effected both by the food chain and by interphase transfer from other media, including air, water and soil (even in the case of their infinitesimal content in these media).[46,165,175,182–195,338] The high stability of these xenobiotics causes their extended retention in natural media and a long period for half-elimination from the organism of animals and man. Toxicokinetic investigations in recent years have shown that for man the *time for half-elimination of dioxin (I) from the organism reaches 6–7 years*[336,337] [for xenobiotics of the (IV) series it is somewhat lower at 1–2 years[339]].

In order to display high toxicity xenobiotics (III)–(VIII), in addition to hydrophobicity and high stability, must possess a high *affinity for their bioreceptor*,[24,77,82–85,317,329,340–343] which is known as the dioxin receptor[83–85,317,329] (although discussion on this problem still continues[344]). They must also have *high biological activity*, expressed as the concentration of substrate causing a 50% increase in the maximum possible cytochrome P-448 activity. All these requirements are possessed by those isomers of the (III)–(VIII) series of compounds containing four chlorine atoms in positions 2,3,7,8. These properties are expressed most clearly in (I) and homologues and analogues close to it in structure which fit into a rectangle of size 0.68 × 1.4 nm^2.

The rate of their *metabolism in vivo* shows an insignificant effect on the toxicity of (III)–(VIII). It was shown for (I) and (II) for example that the rate and direction of metabolism depend on the biological special features of the organism[162–164,195,345] and this process may lead to a less toxic substance.[346] In addition bioactivation in the organism by reductive dechlorination to more toxic substances may occur with Cl_5–Cl_8 derivatives (III).[164]

The diversity of mixtures of xenobiotics (III)–(VIII) actually existing in the environment and the non-equivalence of the toxic action of their individual components hinders assessment of the actual danger of these series to particular objects and regions. It has been proposed that the toxicity of each xenobiotic, chiefly of the (III)–(VI) series, should be cited in terms of a single standard, viz. dioxin (I).[347] For each compound there is a *toxicity coefficient* (TC) relative to dioxin which is determined either by the LD_{50} value,[348] characterising the acute toxicity, or by some more important quality [carcinogenic effect,[349] induction of aryl hydrocarbon hydroxylase (AHH),[350,351] a combination of several effects simultaneously,[352] etc.].[353–355] The TC system enables the toxicity characteristics of any actual mixture of xenobiotics to be reduced to a 'toxicity equivalent' ('*dioxin equivalent*', DE) if the content of each component has been previously determined. In other words, the toxicity of a complex mixture of xenobiotics (III) and (IV) may be expressed through the toxicity of dioxin (I), taken in an amount equivalent in toxicity (in overall dioxin units)¶.

Several TC systems have been proposed[33,347–355,359] and some of them are shown in Table 4 (see also Ref. 347). The complexity of the problem and the non-comparable nature of the initial toxicological packages do not permit the development of a single, generally acknowledged TC system. In the Scandinavian countries and the Netherlands for example a system[348] was used at one time which was proposed in 1982–1983 and revived in 1986 by one of the groups of investigators in the USA. It required the obligatory calculation of the contributions of isomers containing the 2,3,7,8-Cl_4 fragment. Other systems are known which were developed by specialists in the USA,[354] Canada,[352] Switzerland,[353] FRG,[359] by scientists in the northern countries of Europe (the NORDIC system in 1987[355]) and by others.[142,347] A TC system has been described[349] which operates with whole groups of isomers (Cl_4-, Cl_5-, Cl_6-compounds etc.) without separating individual isomers apart from the toxic. An international TC system has been proposed recently.[33] In the main the TC systems developed by various toxicological schools are fairly close (Table 4). Correspondingly assessments of the degree of contamination made using them (as DE) do not differ very much. However critical analysis of the actual approach to assessment of the relative toxicity of various xenobiotics (III)–(VIII) remains fruitful.[360]

Assessment of the degree of contamination of objects by actual mixtures of (III) and (IV) comprises two stages, an analytical and a toxicological. The analytical stage provides separate determination of each component of a mixture in the sample. The danger of the whole mixture (in DE) is assessed in the toxicological stage by summation of its components allowing for the TC of each. To sum up, the DE is found for an actual mixture of xenobiotics expressed in weight units of (I).

Turning to the *medical aspects of the problem* it is noted that the action of (I), (II) and in general any xenobiotic of the (III)–(VIII) series on a living organism (man or warm-blooded animals) is many-sided and depends significantly on the dose of poison, the means of its appearance in the organism, and the age and condition of the organism.[24] Even at insignificant concentrations they cause *suppression of the immune system* and disturb the ability of the organism to adapt to changing conditions of the environment which leads to a sharp suppression of mental and physical efficiency.[324,325] In somewhat higher concentrations they cause *mutagenic, teratogenic* (birth of child-monsters from affected parents) and *embryotoxic effects*, disturbance of the activity of the nervous system, diseases of the liver, digestive tract, etc.[2–18,24,49,86–95,361–364]

The clinical symptoms of disease by xenobiotics (III)–(VIII) are however not clearly expressed and the degree of poisoning by these xenobiotics is not always adequately marked. The appearance of the *disease chloracne* is frequently the first *symptom of heavy poisoning*[88–93,361,365] and in all cases there is porphyria (suppression of porphyrin metabolism). Rapid, progressing emaciation of those affected is observed with heavy poisoning.[24,49,93]

Table 4. Systems of toxicity coefficients of organochlorine xenobiotics of the (III) and (IV) families relative to dioxin (I).

Xenobiotic family	Isomer group	Individual isomers	Toxicity coefficient (TC) from data of						
			(Ref.348)	(Ref.354)	(Ref.353)	(Ref.349)	(Ref.355)	(Ref.33)	(Ref.359)
(III)	Cl_4	2,3,7,8-	1	1	1	1	1	1	1
		Others	—	0.01	0.01	—	—	—	1
	Cl_5	1,2,3,7,8-	1	0.5	0.1	0.2	0.5	0.5	0.1
		Others	—	0.005	0.1	—	—	—	0.1
	Cl_6	1,2,3,4,7,8-	0.03	0.04	0.1	0.04	0.1	0.1	0.1
		1,2,3,6,7,8-	0.03	0.04	0.1	0.04	0.1	0.1	0.1
		1,2,3,7,8,9-	0.03	0.04	0.1	0.04	0.1	0.1	0.1
		Others	—	0.0004	0.1	—	—	—	0.1
	Cl_7	1,2,3,4,6,7,8-	—	0.001	0.01	0.001	0.01	0.01	0.01
		Others	—	0.00001	0.01	—	—	—	0.01
	Cl_8		—	—	—	—	0.001	0.001	0.001
(IV)	Cl_4	2,3,7,8-	0.33	0.1	0.1	0.1	0.1	0.1	0.1
		Others	—	0.001	0.1	—	0	—	0.1
	Cl_5	1,2,3,7,8-	0.33	0.1	0.1	0.1	0.01	0.05	0.1
		2,3,4,7,8-	0.33	0.1	0.1	0.1	0.5	0.5	0.1
		Others	—	0.001	0.1	—	—	—	0.1
	Cl_6	1,2,3,4,7,8-	0.021	0.01	0.1	0.01	0.1	0.1	0.1
		1,2,3,6,7,8-	0.021	0.01	0.1	0.01	0.1	0.1	0.1
		2,3,4,6,7,8-	0.021	0.01	0.1	0.01	0.1	0.1	0.1
		Others	—	0.0001	0.1	—	—	—	0.1
	Cl_7	1,2,3,4,6,7,8-	—	0.001	0.1	0.001	0.01	0.01	0.01
		1,2,3,4,7,8,9-	—	0.001	0.1	0.001	0.01	0.01	0.01
		Others	—	0.00001	0.1	—	—	—	0.01
	Cl_8		—	—	—	—	0.001	0.001	0.001

The *epidemiological consequences of disease* from xenobiotics (III) and (IV) have been correlated in a comparatively detailed manner.[49,88,93,95,158,361,365–397] Data were obtained on examination of cohorts of people involved in industrial accidents and other mass afflictions (FRG,[56,365–368] USA,[147,157,369–373] Italy,[99,152,153,155,374] France,[375] England,[361,395] Japan and Taiwan,[95,120,121,376,377] the Netherlands,[378] Sweden,[379,380] Denmark,[381] Finland,[382] New Zealand,[383,384] Hungary,[385] Czechoslovakia[386–388] and USSR[389–393]) including occupational contact with substances in industry and in agriculture.[158,394–397] For example data are shown in Table 5 on only one group of affected people who were employed in the industrial manufacture of the herbicide 2,4,5-T (XII) and its

¶ The DE system assumes additivity of the toxic action of individual xenobiotics in complex mixtures.[68,356,357] In reality this is not always so and the need to consider synergy (see[68,358] for example) or antagonistic effects already mentioned[132,159–161] remains a practical problem.

Table 5. Illnesses of people linked with the industrial manufacture of 2,4,5-trichlorophenol (TCP) and herbicide 2,4,5-T (XII).

Year	Country	Industrial undertaking, place of manufacture	Manufactured product	Nature of illness	Number of victims	
					total	patients with chloracne
1949	USA	Monsanto, Nitro, Virginia	TCP	Explosion	228	121
1949	FRG	Nordlein, Westphalia	TCP	Industiral contact		17
1952–1953	FRG	Boehringer, Hamburg	TCP	Ditto		37
1952	FRG	Nordlein, Westphalia	TCP	"		60
1953	FRG	BASF, Ludwigshafen	TCP	Explosion	75	55
1954	FRG	Boehringer, Hamburg	TCP, 2,4,5-T	Industrial contact		31
1956	France	Rhone-Poulenc, Grenoble	TCP, 2,4,5-T	Explosion		17
1956	USA	Diamond Alkali Corporation, New Jersey	2,4,5-T	Industrial contact		29
1959	Italy	ISM, Saronno	TCP	Ditto		5
1961	USSR	Ufimsk Chemical Works, Ufa	TCP	Explosion		15
1963	Netherlands	Philips Dofar Amsterdam	TCP	"	141	69
1964	USA	Dow Chemicals, Midland, Michigan	2,4,5-T	Industrial contact	61	49
1965–1966	USSR	Ufimsk Chemical Works, Ufa	2,4,5-T	Ditto	166	128
1965–1968	Czechoslovakia	Spolana, Neratowice	2,4,5-T	"	80	78
1966	France	Rhone-Poulenc, Grenoble	TCP	Explosion		21
1968	England	Coalite Chemical Products, Bolsover, Derbyshire	TCP	Ditto	90	79
1970	Roumania	—	2,4,5-T	Industrial contact		25
1972–1973	Austria	Nitrogen works, Linz	2,4,5-T	Ditto		50
1972	USSR	—	TCP	"		1
1974	FRG	Bayer, Jurdingen	2,4,5-T	"		5
1976	Italy	ICMESA, Seveso	TCP	Explosion		193

technological precursor 2,4,5-trichlorophenol (XIV). Results of studies[35,37,79,88,389–393] were used. Altogether this group includes more than 1000 men having suffered from dioxin (I) in industrial incidents,[97] including at least 8 explosions†. The number of persons suffering from xenobiotics (IV) in connection with massive poisoning in Japan in 1968 and in Taiwan in 1979 exceeded 1850 and 2000 respectively.[95] A large volume of data on poisoning by dioxin (I) contained in herbicide 2,4,5-T (XII) was obtained by systematic examination of American and Australian veterans of the war in Vietnam and members of their families.[143,147–149] All these epidemiological data were obtained from observation of affected people over 10,[61,388,390,395] 15–20[143,373,377,397] and even 30[142,143,368] years after their contact with the xenobiotics and has enabled a more correct judgement to be made on the distant consequences of the effect on people by xenobiotics (III) and (IV).[87,90,93,396,397] As it turned out the symptoms of chloracne continued to be observed on average for 26 years.[394]

The epidemiological consequences of the contact of people with dioxins therefore have a *universal character*. They also occur in the USSR. This may be judged by the data on diseases linked with the manufacture of 2,4,5-trichlorophenol (XIV)[389,390] and herbicide 2,4,5-T (XII),[391–393] which occurred in our country in chemical works in Ufa within the framework of the usual dioxinogenic technology. The experimental output of 2,4,5-trichlorophenol began in 1961 and industrial output of 2,4,5-T in 1965.[393] Fifteen victims were recorded in the manufacture of 2,4,5-trichlorophenol.[389] The first examination of workers contacted in the process of 2,4,5-T manufacture was carried out shortly after its start by the Ufimsk Scientific-Research Institute for Hygiene and Occupational Diseases. Subsequently examinations became regular.[391,392] It became apparent that there were 128 persons with clearly expressed skin disease (serious forms of occupational acne in organochlorine manufacture), characteristic of groups affected in other countries, where there were similar industries, which amounted to 85% total number contacted. Apart from disease of the sebacious follicular apparatus of the skin, accompanying disease of the nervous system, liver, suppression of lipid metabolism, etc. was established.[391–393] Since reconstruction of the plant for the manufacture of herbicide 2,4,5-T from 2,4,5-trichlorophenol did not provide absolute protection for personnel from the development of serious forms of occupational acne and intoxication, the plant was reprofiled to 2,4-D in 1968.[393] Output of 2,4,5-trichlorophenol was stopped in 1987.

It should be mentioned however that there is extreme heterogeneity in the available epidemiological data and there are methodological errors in many investigations. The results obtained for the affected regions of South Vietnam must be considered to be the most objective. These were compared with the ecologically clean regions of North Vietnam. These data fortified by information on the quantitative content of (I) in human breast milk and lipid deposits of people[398] indicate the negative effects of xenobiotics (III)–(VIII) on the life span of the population, on its resistance towards various, especially viral, infections, towards the overall medical situation in the affected regions and towards the child-bearing function of the women. It may be considered that dioxins are one of the most important factors inducing deterioration of the racial stock of several human populations.[35–41]

Decisions have been made on the health and hygiene aspects of the problem of dioxins and related xenobiotics. The impact of these poisons and also the high probability of the appearance and accumulation in nature of dioxin synergists capable of enhancing

† The concentrations of dioxin (I) in vat residues, discovered when investigating the circumstances of these incidents, proved to be extremely significant. It was 2400 p.p.m. in Czechoslovakia, 2000 p.p.m. in USA (1964), 1000 p.p.m. in the Netherlands, 400 p.p.m. in England and 140 p.p.m. in Austria. For comparison it may be noted that the concentration of (I) in soil at the centre of the contaminated zone in Seveso (Italy) was 0.55 p.p.m.[79]

their toxic action,[358] has compelled the health and hygiene services of the industrially developed countries to conduct appropriate investigations. The appearance of dioxin-type xenobiotics in foodstuffs, drinking water and in the air of populated localities is recognised to be inadmissible. However to achieve this while vast quantities of these xenobiotics are circulating in the biosphere, while technology is operating and actually delivering these xenobiotics to the environment, is impossible. At present the problem of limiting the risk of affecting man and nature with dioxin (I) and related substances continues. For this purpose *standards* have been established for admissible *technogenic discharges of xenobiotics* by industry, limiting standards for their *content in the environment* and also standards for admissible '*consumption*' of these substances by *man*.[77,355,399–408]

The limiting standards for admissible weekly and daily consumption by man of dioxin and other xenobiotics of this type (WCD and DCD respectively) are expressed in so-called DE. These are in the form of the weight quantity of dioxin (I) the systematic consumption of which leads to an increase of one victim per million population. Values of WCD and DCD are determined in model experiments in animals by assessing the risk of a teratogenic or carcinogenic effect, immunosuppression, etc. Standards developed by a group of specialists in Sweden, Denmark, Norway, and Finland[355] for the risk of carcinogenicity are: DCD $\leqslant$ 5 pg kg^{-1} and WCD $\leqslant$ 35 pg kg^{-1} which means consumption of $\sim$2000–2500 pg DE in a week for a person of weight 60–70 kg. A similar standard (DCD $\leqslant$ 4 pg kg^{-1}) has been proposed in the Netherlands.[399] In Ontario (Canada) and FRG a DCD $\leqslant$ 10 pg kg^{-1} is considered admissible.[400,404] In USA sizes of DCD for various regions for the risk of carcinogenicity and immunosuppression vary from 10 to 0.1 pg kg^{-1}.[405] On the whole the standards for DCD adopted in the world vary within the limits 0.006 to 10 pg kg^{-1}.[33]

The developed standards for WCD and DCD are used to establish the limiting content of xenobiotics (III)–(VIII) in foodstuffs and in the water, soil and air of the environment. Proceeding from these standards the consumption of fish from internal reservoirs is prohibited, and the consumption of fish from individual farms and milk production from strongly affected regions is limited in some countries. According to the data of the Environmental Protection Agency (EPA) of the USA and of an international group of experts regions containing 1 p.p.b., i.e. 1 μg xenobiotic in 1 kg soil (in DE), are unsuitable for habitation by man. The concentration of xenobiotics in the land of stock farms must not exceed 10 p.p.t., i.e. 10 ng kg^{-1} soil (Netherlands).[402] In Sweden the standard for the limiting content of dioxins in effluent gas for INC under construction is 0.1 ng m^{-3} (for old furnaces a concentration of 0.5–2.0 ng m^{-3} is allowed).[401] In Italy[62] a content of 0.5 ng xenobiotics in 1 m^3 effluent gases is considered admissible, but investigators consider the requirements of the Swedish experts to be correct. In the USA the official standard of the EPA determining the content of dioxins in the air of work places is 0.13 pg m^{-3}.[403]

A general representation is given in Table 6 of the limiting admissible levels of xenobiotics (in DE) which must not be exceeded in the environment and in the surroundings of human habitation in general. This is composed from data of the Italian National Toxicological Committee.[21] More than 10 years study of the problem form the basis for these standards (after the events at Seveso in 1976). The set of standards for the maximum permitted concentration (MPC) of dioxin (I) in air, water, soil, etc. considered by the Minsitry of Health of the USSR has been mentioned[24] as a working alternative for the USSR. It is inconvenient to discuss them at present. However the tentative admissible level (TAL) for dioxin content in water has already been determined by the 'Health Rules and Standards for Preserving Water Surfaces from Contamination', of the USSR Ministry of Health No. 4630-88. This standard is extremely lenient at 0.000035 mg $litre^{-1}$. The fact that the document permits a standard such that the dioxin concentration in water in the USSR will exceed the Italian standard by a factor of 700 000 means that the official standard of the USSR Ministry of Health has no scientific basis at present. In particular it permits without punishment the dumping in only one year of more than 100 kg dioxin (I) in the Ufa river, an absurd amount when it is considered that US airmen sprayed 170 kg (I) in Vietnam in the course of 9 years ('Arguments and Facts', 1990, No. 33).

Table 6. Limiting levels of mixtures of xenobiotics (III) and (IV) permissible in the environment in Italy.[21]

Object	Type of material	Limiting permissible level
Air	Atmospheric air	0.04 pg m^{-3}
	Air in work places	0.12 pg m^{-3}
Water	Drinking, sea, ground water. Reservoir water	0.05 pg $litre^{-1}$
	Community sewer water after purification	0.5 pg $litre^{-1}$
	Community sewer water before purification	50 pg $litre^{-1}$
	Industrial waste water after purification	0.5 pg $litre^{-1}$
	Industrial vat residues	1 μg kg^{-1} (1 ppb)
Soil	Soil in agricultural regions	10 ng kg^{-1} (10 ppt)
	Non-agricultural soil	50 ppt
	Soil in industrial regions	250 ppt
Surfaces	Exterior walls of buildings	75 μg m^{-2}
	Internal walls and surfaces	25 μg m^{-2}

V. Determination of xenobiotics of the dioxin type

The determination of xenobiotics (III)–(VIII) in the environment and in biological samples is a most difficult analytical problem. This is primarily because the toxicological properties of these xenobiotics require that their detection limits in various materials should be substantially lower than those which are typical of many problems of organic analysis, including the determination of pesticides [for example less than 20 years ago the dose of dioxin (I) lethal for guinea pigs was less than the detection limit of the apparatus used for its determination[409]]. No less important is the structural diversity of both the actual substances being determined (see Table 1) and the compounds accompanying them. In other words there is a need to determine all the desired groups of xenobiotics (usually this is tens of substances simultaneously) the individual isomers of which differ principally in toxicity (see Table 3).

The high toxicity of dioxin (I) demanded development and introduction into analytical practice of isomer-selective methods providing detection of picogram (10^{-12} g) and even femtogram (10^{-15} g) quantities, i.e. the determination of compounds with concentrations in the p.p.t. and p.p.q. region.[143,410–436] Data on the dynamics of the reduction of detection limits for dioxin (I) during

the last 20–25 years indicate the important progress achieved in this area. Thus the detection limit of (I) in environmental samples was 1 000 000 p.p.t. in 1965, 50 000 in 1970, 10 in 1975, 0.2 in 1980 and 0.01 p.p.t. in 1983. Similar results have been obtained in the analysis of samples of herbicide 2,4,5-T (XII). The detection limit of (XII) was 1 000 000 p.p.t. in 1965 and 1000 p.p.t. in 1985. Equally significant progress has been achieved in the selectivity of the analytical methods. In 1966 20 isomers of tetrachlorodibenzo-*p*-dioxin, including (I), were determined in environmental samples as one chromatographic signal but already in 1979 it was possible to determine the most toxic isomer, viz. 2,3,7,8-Cl_4-DD, as an individual analytical signal.[105]

Thanks to wide international collaboration many procedures for determining trace amounts of xenobiotics (III) and (IV), including the most toxic, have been devised up to the present time [less for the (V) and (VI) groups as yet[418]]. The application of highly efficient purification of xenobiotics from the multitude of background substances has been proposed and includes their extraction recovery, chromatographic separation and mass spectrometric determination. This progress was provided both by improvements in analytical possibilities by instrumental technique and by the development and standardisation of methods of sample-taking and sample-preparation.

The known analytical procedures (see reviews[86,101–114] and a multitude of papers of recent years[227,414–478]) encompass practically all the important materials, viz. soil and sludges,[100,106,150,413,414,424–427,433,437–440] gaseous media including the air, smokes and exhaust gases and dust particles transported by them, ashes and fogs,[100,410,415,418,421,423,428,435,436,441–447] water,[106,417,424,429,430,432] various surfaces,[150,442,462] industrial goods and waste[413,422,425,429,430,432,441,447,448] and biological samples of vegetable[133,411,479] and animal[151,191,413,414,416,419,420,425,449–452] origin. The choice of actual procedure depends on the problems for the investigator, whether it is necessary to identify the source of discharge of xenobiotics or whether there is a need to assess an actual situation.

Two approaches have been formulated to determine xenobiotics:[102] 1) simultaneous determination of all homologues and isomers in one fraction by enrichment of the component to be measured (separation from the matrix), 2) determination of individual isomers, particularly (I) and (II) which are the most toxic. Both approaches are used for general orientation in ecological circumstances although the first is more useful for monitoring programmes. If the target is the assessment of the dioxin danger of samples and regions then the analytical procedure must be toxicologically oriented [i.e. aimed at the determination of the 12 most toxic isomers of (III) and (IV) out of the 210] and rapid (when biological methods of determination are particularly effective).[111,351,480–484]

Knowledge of the physicochemical, structural and toxicological special features of the xenobiotics under consideration, primarily (III) and (IV), enables the formulation of *general requirements* which any method of determining them in the environment and biological specimens must satisfy.[143] The procedure must provide:

1. high sensitivity, due to the exceptional toxicity of (I) and several other compounds,
2. high selectivity, for which it is necessary to separate the xenobiotics being determined from substances accompanying them in the material the concentration of which may be several orders greater,
3. high specificity providing differentiation of the desired substances within the limits of close mixtures of isomers, particularly the separate determination of the most toxic dioxin (I) in the presence of the remaining 21 Cl_4-isomers of dioxin, etc.,
4. high reproducibility of results on quantitative determination.

The first, second and fourth requirements are provided in a completely satisfactory manner by high resolution mass spectrometry. Differentiation of individual isomers in mixtures is achieved by high resolution gas chromatography.

At the present time only a limited number of analytical laboratories in the industrially developed nations are able to carry out analyses on xenobiotics (III) and (IV) of any degree of complexity, particularly to effect quantitative determination in samples of different types. The short account given below of the state of the analytical side of the problem rests mainly on the experiments of several groups working particularly effectively. They are in laboratories in Sweden and Switzerland,[102,109] USA,[101,103–105,412,413,416,441,458] Italy,[100,106] FRG,[107,108,463,464,466] Canada,[110,439,440,465] Japan,[448] France,[434] Norway[415] and other countries by whose efforts an entire methodology of determining dioxin (I) and related compounds in any sample has been built up.

Several obligatory stages are included in all the various procedures for determining xenobiotics (III) and (IV). These are the taking and preparation of samples, the isolation of the desired substances from the sample, their purification and concentration and finally the correct qualitative and quantitative determination of xenobiotics.

Techniques for *selecting a sample* must be suitable for the character of the specimen. This may be the selection of soil in a volume of fixed dimensions, selection of layers of sludge from two reservoirs, the selection and cutting of vegetables, the collection of atmospheric dust in special containers and large capacity test-samplers, wipes of dust or scraping of the upper layer of solid surfaces, the absorption of substances from water, the taking of test samples of ground or surface water and, finally, the specialised selection of biological specimens of animal origin (selection of fluids, organs and tissues). The *preparation of samples* also includes several operations, viz. sifting (soils), drying (soils and sludges), lyophilisation (biological substrates) and acid treatment (water, soils, sludges) and alkaline treatment (vegetation, residues, biological substrates).[106]

When selecting samples the problem of the amount required arises since the detection limit of the desired group of substances must be provided at the p.p.t. level and at the same time the possibility of erroneous results appearing must be avoided. In principle a detection limit of 1–10 p.p.t. of dioxin (I) may be successfully reached with a test sample of 1 g. This is particularly important for biological samples of animal origin, such as blood, milk, lipid tissue, etc. Otherwise one is obliged to deal not only with large amounts of sample but also with the hazard of the large effect of the matrix. The problem of volume is less pressing for samples of air, water and soil (discounting the role of the matrix). For the detection of femtogram quantities of (I) in air it is possible, for example, to take a sample from a volume of 1000 m^3.[415]

Recovery of xenobiotics and their subsequent purification is carried out in such a manner that the substances being determined are not lost in this process and not formed anew. This is provided by introducing into the test sample one or several internal standards from a number of compounds of types (III) and (IV) labelled with ^{13}C, ^{14}C, ^{3}H or ^{37}Cl.[106,141–143,413,485,486]

The mixture of xenobiotics is *recovered* from a sample, as a rule, by extraction with an organic solvent such as hexane, benzene, toluene, chloroform, dichloromethane, petroleum ether, etc. or solvent mixtures (hexane/acetone, chloroform/methanol, dichloromethane/cyclohexane etc.). Dimethyl sulphoxide has proved to be very effective.[425] Extraction is carried out with manual or mechanical shaking (suitable for substrates of all types) or in a Soxhlet apparatus (soil particles and air dust). The degree of recovery of the standard is usually 70–80%.[429] The more firmly the desired xenobiotic is bound to the matrix the worse is the recovery. The action of ultrasonic vibration on the sample (soil, water sludges),[106,487] absorption on polymeric resins (water, air)[106,417,423] and extraction using supercritical liquids[440] are used to increase the completeness of recovery of xenobiotics.

Various methods are used for the *purification of extracts* such as redistribution from one solvent system to another, and multistage purification using chromatographic techniques (columns, gel chromatography, high performance liquid chromatography, HPLC, etc.). The procedure for the purification of environmental samples calls for multiple chromatography (on pure silica, silica modified with sulphuric acid and on alumina), which provides recovery of all substances of types (III) and (IV) at a content of (I) at the level of 1–10 p.p.t.[100,141] Purification of biological and environmental samples is more effective using chromatography on activated carbon,[413,485] which preferentially retains planar polynuclear hydrocarbons. The effectiveness of the specific recovery of the latter by activated carbon is confirmed by comparison of the various methods of purifying (I) (on determining its content in fish)[486] and the other xenobiotics (III) and (IV).[103] Extracts of lipid tissue or samples of animal or vegetable origin are purified from readily decomposing organic substances by treatment with concentrated sulphuric acid. Generally the total process for purifying samples includes at least six procedures. These are purification on a column of the extrelut type (biological substrates), on silica gel (samples of soil and plants), on a column of Florisil (majority of substrates), on a column of aluminium oxide (majority of substrates), treatment with acid (majority of substrates) and with acetonitrile (samples with a high fat and oil content).[106]

When purifying extracts by a chromatographic technique their *concentration* and preliminary separation is effected simultaneously.

Analysis of a sample includes the determination in the purified extract of individual groups of xenobiotics (III) and (IV) (for example all 2,3,7,8-Cl_4-containing homologues and isomers, all Cl_4-isomers of DD or DF, all groups of isomers of Cl_4-, Cl_5- and Cl_6-DD, etc.) or the separate determination of each component of a mixture, especially the most toxic. This is achieved by the sequential use of chromatography and quantitative mass spectrometry, including high resolution. Occasionally their direct combination is used, for example by connecting the chromatographic column directly to the ion source of the mass spectrometer. Depending on the combination taken and the frequently fairly complex procedure each stage of the analysis (sample preparation, its introduction into the mass spectrometer, and finally the mass spectrometric determination proper) may be assigned to virtually one of three classes, viz. low, medium and high resolution. Correspondingly it is possible to effect in practice a very large number of independent procedures each of which provides resolution of an actual problem.[105]

High resolution chromatography is used for the *separation of individual isomers in mixtures*.[143] Separation of xenobiotics is carried out by temperature programming on capillary columns, prepared from glass or fused quartz, of length up to 60 m (internal diameter of the order of 0.25 mm). Silar 10C, OV-17 and OV-101, DB-5 or DB-225, SP-2330, SP-2331 and SP-2340, SE-54, CP Sil 88, SILOV, etc., are used as stationary phases.

A quadrupole mass spectrometer is used in the gas chromatographic-mass spectrometric determination of xenobiotics. Ionisation may be effected by two means, by electron impact (EI) and chemical ionisation. Ionisation by EI (ionisation conditions are up to 70 eV, 250 °C) is most suitable for Cl_4-derivatives of (III) and (IV).[137] The detection limits of 1–10 pg for Cl_4-xenobiotics (III) and (IV) and 10–50 pg for Cl_8-compounds are achieved using single and multi-ion detectors (SID and MID). To obtain a complete mass spectrum 0.1–1 ng substance is required.[109] Negative ion chemical ionisation (NCI) using methane as reagent (0.35 Torr, 180 °C) provides high sensitivity of determination of all furans (IV) with $x + y = 4$ to 8 and also of dioxins (III) with $x + y \geqslant 5$ [i.e. highly chlorinated dioxins except for (I)]. The sensitivity of this method using SID detection is 10–100 fg, i.e. 1–2 orders of magnitude greater than on using ionisation by EI.[143] The NCI technique using O_2 as reagent requires construction of a special ion source.

The use of high resolution mass spectrometry provides a further increase in selectivity and sensitivity. In particular at a resolution of 5000–10 000 using EI and SID techniques a sensitivity of 10–200 fg is achieved, which is improved for xenobiotics (III) and (IV) with the progressive transition from tetra- to octachloro derivatives.[109]

A mass spectrometric detector (mass fragmentography) is used for the *quantitative* mass spectrometric *determination* of xenobiotics (III) and (IV). The precision of determination is provided using isotopically labelled standards. This is particularly important in cases when the concentration of the desired substances in the sample is at the p.p.t. level or below.

A principal step in the determination of xenobiotics (III) and (IV) is the creation of *isomer-specific* methods of identifying and quantitatively determining individual isomers in mixtures.[102,143,216,225,276,298,448,463,465,467] The mass spectrometric method does not provide determination of individual isomers [the spectra of the majority of isomers in each of the mixtures of compounds of both types (III) and (IV) proved to be similar]. The need to determine individual isomers is dictated by the principal differences in toxicity of the individual xenobiotics forming the large series of isomers.

The possibility of separating individual isomers, such as the most toxic, is provided by a combination of high resolution gas chromatography with subsequent mass spectrometry for the quantitative determination of the separated isomers. High resolution GLC with a glass capillary column of Silar 10C (cyanosiloxane phase) is used for the separation of the most toxic isomer (I) from the remaining 21 Cl_4-DD isomers.[225] The separation of toxic dibenzofuran (II) from the remaining 37 Cl_4-DF isomers is achieved by several procedures, including capillary GC with a smectic liquid crystalline phase.[463,464] A procedure has been described for the identification of individual dioxin isomers (III) [in each of the series of (III) with $x + y = 4$ to 8] with Silar 10C[225] and SP-2330[298] columns and with activated alumina.[467] A method of identifying each of the 38 isomers of Cl_4-DF in mixtures of them has been described and was achieved using capillary columns of SP-2330 and SE-54.[217] Separation of the majority of isomers in mixtures of Cl_4-, Cl_5- and Cl_6-DF using SP-2330 columns has been reported.[298] This is particularly important when it is necessary to separate such pairs of isomers as the toxic 1,2,3,7,8-Cl_5-DF and the less toxic 1,2,3,4,8-Cl_5-DF and also the toxic 1,2,3,4,7,8-Cl_6-DF and the less toxic 1,2,3,4,7,9-Cl_6-DF which are usually eluted unseparated. Such a separation was achieved on OV-17 and DV-5 columns.[143]

The use of high resolution techniques is obligatory if xenobiotics (III) and (IV) are present in a sample at the background level. It has been shown in practice that at such low concentrations erroneous results may arise and to exclude this it is necessary to apply different methods simultaneously.[105]

Table 7. Limits of detection of dioxin (I) in various samples taken in the Seveso region.[106]

Sample type	Sensitivity, ppt	Chromatographic and mass spectrometric technique for determination
Water	$\leqslant 0.01$	Standard or high resolution
Air dust	60–200	High resolution
Vegetation	$\leqslant 1$	Ditto
Biological media	<100	"
Soil	$\leqslant 1$	"
Sludges	<100	Standard or high resolution
Solid surfaces	<10 ng m^{-2}	Ditto

Some successes in the determination of xenobiotics achieved in the last 10–15 years are reflected in Table 7. The detection limits of dioxin (I) given in it were obtained using standard analytical techniques when investigating samples selected in the Seveso (Italy) region after the accident in 1976.[106] Numerous correlations of that type pertaining to the whole range of possible analytical problems in the determination of xenobiotics (III)–(VIII) have been collated.[104,105]

There are definite differences in the set of procedures for determining (III)–(VI) in natural samples associated mainly with sample selection, sample preparation and the purification of extracts.[106]

Since xenobiotics are mainly in the absorbed state in *water* bound to colloids and soil particles and to a much lesser extent in the free state, their mobility is determined by the mobility of these particles. To extract xenobiotics from water samples a mixture of saturated hydrocarbons is used such as hexane–acetone (4:1) or hexane–dichloromethane. Later, samples to be analysed were passed through an absorbent material from which the samples enriched with xenobiotic were extracted with a suitable solvent such as ethyl ether. Most frequently chromatographic filtration through a column of alumina sometimes at low pressure is used for purification. Chromatography using a column with a multilayer packing or a column of Florisil remain the standard methods of purification.

Hundreds of milligrams of sample are collected when analysing *atmospheric dust* at low dioxin (I) concentrations. This is achieved using special vessels for the passive collection of dust (for a period of the order of 30 days) or high volume samplers. Attempts have been made to use electrostatic precipitators (their drawbacks were poor reproducibility of results, dependence on atmospheric moisture, a requirement for special positioning and maintenance). At the end of sample collection atmospheric moisture absorbed incidentally was separated by filtration and analysed by the specification for the analysis of water. The solid was dried for 24 h, after which xenobiotics and accompanying substances were extracted with a hexane–acetone mixture (4:1). Particles collected on the glass fibre filter of a high volume sampler were recovered in a similar manner. The extract was purified on a multilayer column and a column of alumina. Dioxin (I) and related compounds were determined in the extract by GC-MS.

In the analysis of *vegetation* it is assumed that dioxin (I) settles on the surface of samples and is there in a mobile form. Consequently in the seventies dioxin was simply extracted from grass without previous treatment and subsequent purification. More recently it has become clear that xenobiotics may also pass into plants from the soil and their level in plants may be comparable or greater than the levels in the environment. Since xenobiotics are bound to internal tissues of plants more firmly than to their surfaces after settling out of the atmosphere, samples are subjected to alkaline treatment with subsequent extraction. Three stages at least are used for the purification of (I). These are filtration through a multilayer column, through a column of Florisil (magnesium silicate) and finally through a column of alumina. In some procedures these three stages are preceded by filtration through silica gel which is required to retain highly polar compounds. The use of high resolution techniques increased the selectivity of determination. The procedures devised enable (I) to be determined in various plant organs.

When determining xenobiotics in domestic and wild *animals* data are obtained not only on their content but a correlation is found with the levels of their content in the environment (bioconcentration) as well. Previous treatment of biological samples includes alkaline hydrolysis with subsequent extraction with hexane. The extract is purified through a multilayer chromatographic column and through a column of the extrelut type. Xenobiotics have been identified and quantitatively determined in many samples using the usual GC-MS technique.

The analysis of *soil* for content of dioxin (I) and related xenobiotics was initially carried out by extraction with dichloromethane without preliminary treatment. Later an additional step has been introduced, viz. treatment with sulphuric acid and chromatographic filtration on a column of alumina, then an additional filtration on a column of Florisil. Purification with acetonitrile has also been applied. Solvents or mixtures containing no dichloromethane are used for extraction, the most effective being a hexane–acetone mixture (4:1). These preliminary purification stages enable an increase in the sensitivity and selectivity of the analysis particularly when using high resolution techniques.

As a rule the content of xenobiotics in water is below the detection limit. However they are found in *sludges*, mud and finely dispersed particles. Procedures for the analysis of sludges are similar to the procedures used for the analysis of soil. Usually sludges, mud and finely dispersed particles are first treated with acid or alkali to decompose mineral components and accompanying organic substances. This increases recovery of xenobiotics from the liquid extract. An alternative route is the drying of the sample and subsequent extraction of xenobiotics from the solid substrates.

Cotton pads moistened with a hexane–acetone (4:1) mixture are used for the collection of test samples containing dioxin (I) and related compounds from smooth, hard and non-absorbent *surfaces* (pottery, glass, tiles, plastic, varnished articles of metal and wood, etc.). To establish the degree of contamination of buildings wipes are taken of the walls, floors and windows (usually from areas of 0.5×0.5 m^2). The outer surfaces of buildings are examined by scraping

(1–2 mm) a square of surface 0.1–0.25 m^2 of the outer layer of the wall. Xenobiotics are extracted from cotton pads and scrapings with a mixture of hexane–acetone (4:1). Purification of the extract consists of acid treatment using a multilayer column and chromatographic filtration on alumina. Occasionally a column of Florisil is applied for intermediate purification. Detection and quantitative determination of xenobiotics is carried out by GC-MS.

Turning to the *overall organisation of analyses* of xenobiotics (III)–(VIII) it must be emphasised that this work is accompanied by considerable methodological and technical difficulties. Even within the framework of already established systems, i.e. essentially running, these analyses are extremely expensive, laborious and of long duration (as a rule they occupy many days). In addition the conduct of such analyses requires the use of special premises equipped with allowance for the very stiff requirements for accident prevention.[453–455] Because of the high toxicity of xenobiotics it is necessary that analytical samples separated for such analysis are not used for other purposes. It is also necessary that specially pure solvents, reagents and materials are used. In particular when taking air samples polyurethane or Teflon-coated glass-fibre filters are required together with polyurethane stoppers.[415,435,436] Finally the scale of carrying out analyses demands the organisation of the manufacture of standards. At present methods have been developed for the synthesis of each of the 210 xenobiotics of the (III) and (IV) series.[198,215–220,223,472]

Although many of the difficulties indicated have been overcome there are still often cases when analyses of a single specimen have been completed with serious deviations. To prevent similar errors interlaboratory comparative determinations are carried regularly in the industrially developed countries which enables comparison and standardisation of procedures.[150,419–422] The so-called 'method 8290' has been proposed for the same purpose, which enables, according to the ideas of its originators, the same results to be obtained in different laboratories by standardisation of the determination procedure.[478]

Work continues on the *improvement of techniques for the determination* of xenobiotics (III)–(VIII). Two main directions are planned. The first concerns the improvement of methods known already. Special extractors are being developed enabling the practically complete recovery of xenobiotics from soil, sludges and other materials.[426,440] Analyses are optimised both in the stages of separation of xenobiotics and in their determination. In particular computerised systems have been devised for the quantitative assessment of the results of gas chromatographic-mass spectrometric determination of xenobiotics.[468–470] Work is being conducted on the design of analytical techniques adapted for direct measurements under field conditions. For example a mobile mass spectrometer has been built in FRG which enables the direct determination under field conditions of dioxin (I) (in subnanogram quantities) and certain other highly toxic substances.[477]

The second direction concerns the development of new approaches to analysis brought into existence both by the laborious nature of the determination of xenobiotics (III)–(VI) within the framework of traditional methods and by the need to obtain express information on an actual epidemiological situation. Attempts have been made to develop *biological*, particularly immune, *methods of determining* and immediately *testing samples*.[111,351,480–484] Several biological substrates capable of specific and sensitive reaction with (I) and related xenobiotics have been proposed for biotesting (chick embryos, certain blood and sheep cells, etc.). The selective absorption of (III) and (IV) from the environment by certain flora[193] (leaves[488] and fir needles[194,489]) and fauna may be used for biotesting.[490] A radioimmunoassay has been developed for determining dioxins (III) in fish (Canada).[484]

The use of monoclonal antibodies for the immunodetermination of (III) and (IV) is particularly promising.[113,114,480] A set of antibodies has been isolated which provides a specific reaction with the highly toxic tetra- and pentachlorinated xenobiotics (III) and (IV) with lateral 2,3,7,8 disposition of chlorine atoms. These antibodies do not react with substances usually present (phenols, polychlorinated biphenyls, herbicides including 2,4,5-T, etc.). The determination of xenobiotics (III) and (IV) in material of various types, such as light ashes, motor oils, vat residues, etc., leads to satisfactory results (confirmed by correlation between data of immunodetermination and of normal GC-MS). The method provides detection of 0.5 ng dioxin (I). In our opinion this direction for analysis, in spite of several limitations, may provide a sharp drop in the consumption of time and money in the determination of samples of various types and forms a basis for effective monitoring in a practicable time scale.

VI. Environmental contamination by xenobiotics of the dioxin type. Monitoring

Problems of the chemistry of dioxin (I) in the environment[74] and the general global approach to the assessment of world-wide contamination of the biosphere by xenobiotics (III)–(VIII)[75,491,492] are still only being worked out. The previous attempt to solve this problem, accomplished in the study of the global contamination of nature by organochlorine insecticides, may only be used to a small extent. Thus xenobiotics (III)–(VIII), like the highly lipophilic organochlorine insecticides, accumulate readily in the organic phase of the biosphere and are redistricted along the food chain,[142,143] i.e. efficient participation in biotransfer is common to these two types of contaminant. At the same time the special features of the physical and chemical properties and the toxicological characteristics considered above determine the singularity of other routes of transfer of (III)–(VIII) in nature. Cases are already known at present of the efficient vertical migration of dioxin (I) in the lithosphere which determines the probability of contaminating water-bearing soil layers with it. The tendency to form stable molecular complexes in the organic phase of soils leads to an unusual, depending on soil-climate features, route for the horizontal migration of compounds (III) and (IV) in the lithosphere and to the effective conduct of transfer across boundaries. In this way modelling of the behaviour of (III)–(VIII) in nature is an incomparably more complex problem than for the organochlorine pesticides. It is made many times more complex by the extreme diversity of the homologues and isomers of (III)–(VIII).

It is known that monitoring is the most effective means of establishing the real situation for the contamination of the biosphere and is the basis for developing programmes for protecting regions, objects and populations. It is classified as chemical, biological and toxicological depending on the methods used. *Chemical monitoring* is effected by chemical, chiefly instrumental, methods. It has the purpose of recording territorial changes in xenobiotic concentration with time. *Biological monitoring* is aimed at the search for possible diseases of man and living organisms in general. *Toxicological monitoring* relates to the analysis of temporary effects of affected populations.[357,493]

The methodology of studying contamination of the biosphere by xenobiotics (III)–(VIII) comprises several parallel routes of investigation.

Firstly the methods of chemical and biological monitoring enable the *accumulation of information* on the distribution of these xenobiotics between various parts of the environment. Thus in recent years xenobiotics (III) and (IV) have been detected and determined in many new specimens such as reservoir sludges,[494] air and rain water,[172] sea and fresh-water life,[495] food products,[496] human tissue,[332,333] etc. At present there are data on the composition and content of xenobiotics (III)–(VI) in practically all parts of the biosphere: in water,[165,269,497–500] in soil and sludges,[253,304,500–506] air,[172,255,304,348,415,423,435,436,494,507–509] vegetation,[479,510] fish,[484,485,495,511] organs and tissues of warm-blooded animals,[142,143,191,332,333,495,512–518] human milk,[514,519–523] foodstuffs[141, 142,496,502,511,514,524–527] and technical products.[306,447,528] Several reports have been devoted to a study of the content and routes of migration of xenobiotics (III) and (IV) in animate and inanimate nature.[53,54,137,304]

Secondly the *geographical features* of the formation and distribution of (III) and (IV) in nature are assessed by monitoring methods. As already indicated above the composition has been studied and a quantitative assessment made of the discharge of xenobiotics when operating INC in practically all industrially developed countries of the world. The same applies also to the assessment of discharges from other sources and to the study of their content in the environment of various regions of human habitation. Such investigations have been conducted in USA,[348,453,507,521,529] Canada,[352,498,524] FRG,[300,500,501,514,519,527] Japan,[497,499,506,512,513,521] England,[63,505,510,520] Italy,[100,106,153,155,156] Sweden,[301,511,530] the Netherlands,[141] France,[531] New Zealand,[303] etc. The number of scientific laboratories occupied with this problem is growing continuously and is more than one hundred at present (47 in USA, 23 in FRG, 12 in Canada, 9 in Italy, 7 in England, 5 in the Netherlands, etc.).[33]

A particular approach to making contaminated regions apparent and clarifying the extent of their contamination is based upon the use of *data on sources* of xenobiotics (III)–(VIII). For example the total quantity of chlorophenols manufactured by the industrially developed nations is known (150 000 tons annually[63]) as is the territorial disposition of manufacture and the content of xenobiotics [predominantly of the (III) type] in each of the industrial products. In particular 99 places of manufacture of 2,4,5-trichlorophenol (XIV), of its use as a raw material in pesticide production and of the burial of poisonous waste are known and 17 of them are considered to be particularly dangerous.[532] The throughput and territorial distribution of INC are also known (2000 in Japan, 47 in FRG, 25 in Sweden,[22] 45 in Denmark,[280] 22 in northern Belgium,[273] etc.). The overall dimensions of the discharge of xenobiotics by these furnaces and the typical distribution in them of the most toxic homologues and isomers are also known. Finally the levels of consumption of ethylated petrol by the motor transport of various countries, their compositions and discharge volumes of (III)–(VIII) are known.

Allowing for these sources attempts have been made to assess the total volume of discharges and contamination by xenobiotics (III) and (IV) for actual territories and also the *dynamics of contamination* as a function of various factors. Existing experimental data on the similar ratio of homologues and isomers discharged by INC in industrially developed nations of various regions (Canada, Japan, France, Norway, etc.), regardless of the dependence on combustion regimen and the composition of the materials being destroyed,[283] was used as was data on the approximate similarity of the isomer–homologue composition of the xenobiotics discharged by various sources such as INC and motor transport.[304] However such approaches are not always reliable. In particular the hypothesis of the close relationship of homologues of (III) and (IV) present in the air in molecular form and absorbed onto aerosol particles has not been confirmed.[304] It turns out that particles transported by the air absorb the highly chlorinated (less volatile) homologues to a larger extent, thus effecting a forced separation which is not always favourable toxicologically.[172] It is also difficult to judge the quantities of xenobiotics (III)–(VIII) formed from their precursors in nature. For example the direction of the photodechlorination of the weakly toxic octachlorodibenzo-*p*-dioxin on a soil surface differs markedly from model conditions in solution. In nature a portion of the isomers of tetra-, penta- and hexachlorodibenzo-*p*-dioxin is formed by fission of *peri*-chlorine atoms, i.e. accumulation of highly toxic isomers with a 2,3,7,8-tetrachloro fragment occurs, while in solution chiefly lateral chlorine atoms are lost.[206]

It is important to know the detailed characteristics of individual suppliers of xenobiotics (III) and (IV) to bring about international cooperation on the problem of monitoring dioxins, since different sources may prove to predominate in individual countries.[63] Thus contamination of the English environment arose predominantly by the yearly inflow of xenobiotics from the manufacture and use of polychlorophenols [4.5 kg xenobiotics (in DE) from a yearly manufacture of 2000 tons chlorophenols].[63] The main sources of xenobiotics (2 kg) entering the environment in the Netherlands each year are INC.[533] In Norway the annual discharge of xenobiotics in waste water by only one metallurgical undertaking was 0.5 kg.[291]

The *integration of contributions to the contamination* of the environment by various sources of (III)–(VIII) enables assessment of the overall situation in any region and exposes the most dangerous technologies. For example assessment of the discharge of xenobiotics in Sweden in 1987 appeared as follows (in DE): combustion of domestic refuse 200–300 g, discharges from metallurgical undertakings 100–200 g, motor exhausts 10–150 g, etc. (about 1 kg in all).[534] In Canada, where discharges are more significant and contributions to the integrated contamination from individual sources are reduced year by year depending on industrial politics,[63] the following data were collected in 1986 (in Ontario province,[400] in DE): by combustion of rubbish in INC and the rendering harmless of waste water 8–10 kg, other forms of combustion 20–50 kg, impurities in polychlorobiphenyl > 4 kg, trans-border transfers (from USA) 2–20 kg, etc. Similar assessments have also been carried out for all Canada.[535] One further example of the integrated approach is the assessment by Swedish scientists of the overall content of xenobiotics in the sludges of the Baltic Sea accumulated from the whole industrial history of the region (the quantity of xenobiotics was 30 kg).[534]

When assessing *products of individual technologies* as sources of xenobiotics (III)–(VIII) it is important to know whether they are only carriers or carriers and precursors of contamination in nature. The degree of danger of a product of the first series is determined by the content in it of toxic microcontamination since the products themselves are usually effectively biodegraded in nature.[326,330] At the same time the danger of potential precursors of dioxins is not just their adequate microcontamination content since some routes for their metabolism, determined by the biological activity of the medium into which they enter, may lead to additional accumulation of dioxins in nature.

For instance paper is a product used by man in his way of living and is only a carrier of xenobiotics (III)–(VIII). Xenobiotics (III)–(VIII) are found in coffee filters, wrapping paper, paper napkins, childrens' napkins, etc.[247] Domestic use of paper is inevitably accompanied by transfer of xenobiotics directly into food (coffee, milk, butter, tea, etc.) and then into the organism.[247,536–538] The use of dioxin-containing paper is particularly dangerous for childrens' napkins, sanitary tampons, handkerchiefs, etc. since skin layers and mucous membranes extract the xenobiotics from paper.

Examples of products of the second series are polychlorophenols, polychloroanilines and their numerous derivatives, including azo and azoxy derivatives, certain polychlorobiphenyls, polychlorobenzenes, hexachlorane and other products. The manufacture and use of such products is inadmissible according to the concepts of the Environmental Protection Agency of the USA. Their danger for the contamination of nature may only be established experimentally by monitoring for dioxin.

Much attention has been paid in modern investigations to the process of transfering xenobiotics (III)–(VIII) in nature and their crossing from one phase to another. It has been shown that in air[539,540] and in water[541,542] various families of high molecular composition serve as carriers of xenobiotics. The main transport media for the transfer of xenobiotics are air and water and the atmosphere provides a more effective transport of xenobiotics from sources to an accumulating medium (or object).[174,175,494,539,540] The role of soil in the long-distance transport of xenobiotics is significantly less,[204] although our knowledge of the mechanism of the interaction of xenobiotics with the soil surface and sludges is hard to call exhaustive.[541]

When considering the problem of the *global transport of xenobiotics* it is necessary to pay attention to the principal differences between the three processes by which xenobiotics (III)–(VIII) cross from one phase to another, viz. the crossing of xenobiotics from their sources of manufacture to the environment, subsequent crossing from inanimate nature to flora and fauna, and finally, their return to inanimate nature from higher organisms. In the first case practically no changes occur in the composition of mixtures of xenobiotics. The ratios of homologues and isomers characteristic of their sources are mainly retained in inanimate nature. Only small changes are possible, explained by differences in the physicochemical properties of the xenobiotics.[283,300,543]

The picture changes sharply in the second process. Representatives of flora and fauna are particulary efficient in retaining xenobiotics with a 2,3,7,8-fragment by *bioconcentration*.[141,195,513,514] Within the homologues of this type as was made clear on analysis of the tissue of people living in different regions of the world, such as USA, Canada, Europe, and Japan,[332,333] no differences were observed in the ratio of xenobiotics. Selection is regulated in absorption concentration by the number of halogen atoms (it is most effective when $n = x + y = 8$) and accumulation during bioconcentration is effected with a toxicological orientation. It is also evidently impossible to ignore the special features of individual organisms with regard to efficient absorption of different types of xenobiotics. For example it was discovered recently[491] that the grampus concentrates xenobiotics mainly of the furan series (IV) and polychlorobiphenyls but compounds (III) are found in insignificant quantities.

When carrying out the third process, i.e. in the return *crossing of xenobiotics from higher organisms to inanimate nature*, the tendency is reversed. In biodeconcentration the most toxic xenobiotics with a 2,3,7,8-fragment effectively do not emerge from living organisms or only emerge from them as a final event.[141,544]

Precisely these features ensure that human disease by dioxins effectively occurs through the *food chain*. In this case only the most dangerous xenobiotics of the (III)–(VIII) series are consumed. The non-toxic isomers, many of which possess the properties of antagonists of (I) and (II), are selected out in the biotransfer process. Hence increased attention is being paid in practically all the industrially developed nations to the problem of analysing dioxins in foodstuffs, to the problem of manufacturing ecologically pure food and to the search for new safe foods.

Turning to biological monitoring for xenobiotics in the biosphere we note once again that the main source of their entry from the environment (soil, water and air) into man and animals is the food chain. Fish and dairy cows must receive a special mention of all the known concentrators of dioxins.[141,165,174,188,191] Xenobiotics transfer from fish to man (or to animals and birds eating them[141]) directly and from cows chiefly through milk.[175] It has been established[334] for example that xenobiotics accumulate efficiently in the milk of cows (in the lipid fraction[141]) grazing close to INC and in people using this milk (accumulation occurs more than 2 orders of magnitude more efficiently than on directly inhaling air from an INC[334]). The rate of absorbing xenobiotics from the oesophagus into animals[545] and later of transfering them into milk[338] is very high. Xenobiotics enter the offspring from the mother not so much through the placenta (natural protection operates) but more through the mothers' milk[321] and then through the oesophagus.[545] In this connection the World Health Organisation has developed an international programme on the dioxin problem in human breast milk in which practically all the industrially developed nations are involved.[141,514,520]

A detailed investigation by Swedish scientists[142] and by others[519–523] of the accumulation of dioxin in breast milk has shown that the content of xenobiotics (III) and (IV) in milk correlates with their concentration in the lipid tissue of the mother though they enter the lipid tissue from food, drinking water and the air. Direct transfer of dioxins into man through the integument from contaminated water and soil is also possible. The danger of infants being affected by dioxins is determined by the extent of the contamination of nature. Thus in 1970 there was a level of 0.8–1.45 p.p.b. of xenobiotics of type (III) in the milk of nursing mothers in South Vietnam. A large quantity of dioxins (16–30 p.p.t., in DE) was found in the maternal milk of women living in industrially more developed countries such as FRG, Belgium, Japan, the Netherlands, England, etc. The highest concentrations of dioxins (up to 30 p.p.t.) were observed in the milk of women living in huge industrial centres such as Hamburg (FRG). The first data on the dioxin content of maternal milk of inhabitants of the USSR have recently become known (obtained by scientists from USA and FRG).[546]

In conclusion it must be mentioned that monitoring of dioxin xenobiotics may be both universal and thematically or territorially oriented from the point of view of organising and financing the work.

Programmes accomplished in the USA[326,547] and Sweden[530] may be considered as examples of *universal monitoring*. The programme initiated in the USA in 1975[326] specified the carrying out of a huge series of determinations of xenobiotics in various samples in all regions of the country. Many state, industrial and university laboratories were involved. In 1983 the programme grew into a 'National Dioxin Strategy' conducted according to an assignment of

the US Congress[547] in seven main directions and emerging beyond the limits of just monitoring. In Sweden beginning in 1988 it is planned to carry out a 2.5 year universal monitoring consisting of 1000 analyses of various samples for content of xenobiotics (III) and (IV) and also of PCB, PBB and polychloronaphthalenes. The programme comprises a combination of chemical and biological methods of analysis and the samples include food, air, certain sediments, paper, INC discharges and biological specimens. The first 400 analyses were completed in 1988.[530]

Monitoring for xenobiotics (III) and (IV) is laborious and expensive (the cost of each determination including sample preparation comes to \$2000–2500[453]). In 1985 the cost of monitoring for these xenobiotics in the USA exceeded \$150 million.[63] The expenditure in Canada on monitoring up to 1985 reached \$6 million.[254] Large appropriations for similar purposes have been made in FRG[242] and Japan.[275]

Programmes for thematically and regionally oriented monitoring have been carried out regularly in the industrially developed nations. Examination of soil around Seveso (Italy) after the accident in 1976 is being continued,[156] the monitoring of regions near known 'dioxin dumps' is being carried out (Netherlands,[313,314] FRG,[311,501] USA[308–310]). In recent years vast programmes have been put into operation to study soil[505] and plants[510] in various regions of England, the 'supply baskets' of Canada,[524] FRG[527] and other countries are being examined. The toxicological monitoring of groups of people having, or having had in the past, 'contact' with xenobiotics (III) and (IV) is gradually beginning (USA[17,147,157,158,515] Japan,[95,96] Vietnam,[516,523] etc.).

Although the results of these programmes are considered to be satisfactory on the whole some alarming facts have been recorded. The analysis for xenobiotic content of fish caught in various Swedish waterways had led to the conclusion that the weekly consumption of Baltic Sea codfish in individual parts of the country exceeded the value of WCD taken as acceptable.[511] The weekly consumption of dioxins through food in West Berlin was 1.3 pg kg^{-1},[527] which is greater than the standard taken to be acceptable in some countries.[33]

VII. Prevention and destruction of dioxin contamination

Large scale measures to limit anthropogenic danger caused by xenobiotics (III)–(VIII) are being put into operation by the technically developed nations. These measures are effected in three main directions.

The first concerns the *improvement of the operating technology* whereby xenobiotics are no longer generated or their discharge is reduced to safe levels. In particular work is being carried out on modernising cellulose–paper industrial undertakings in Sweden,[548] USA[251] and other countries. New technology is being introduced for bleaching cellulose pulp which is accompanied by practically no formation of xenobiotics (III) and (IV),[548] and paper free from dioxins has already begun to be produced. Especially strict control has been established for paper for children.

Programmes have actively been put into operation for restricting the discharge of xenobiotics to the environment from the numerous INC in Sweden,[549] Japan,[275,278] Canada[254,255] and other countries. The introduction of technical improvements into the process of burning waste has provided minimum formation or even complete destruction of xenobiotics. This concerns the construction particularly of new INC.[255,259,289] An economical INC has been developed enabling elimination of xenobiotic formation in the process of burning domestic refuse.[550] A procedure has been found for destroying xenobiotics by passing the exhaust gases and light ash from the INC over a catalyst. In this case destruction of dioxins occurs almost completely even at 350–450 °C.[551] Equipment is widely used to remove xenobiotics from INC discharges and includes filters[272] and electrostatic precipitators.[552,553] In addition it is considered that the cardinal solution to the problem of destroying solid domestic waste requires prohibition of processing it without separation and use of components of the rubbish as secondary raw material.

The selection and manufacture of organochlorine compounds is being modernised in chemical undertakings. In the industrially developed nations the manufacture and application of chlorinated products, which are precursors of dioxins in nature, is prohibited. This primarily concerns 2,4,5-trichlorophenol and pesticides based on it.[49,142] In any case apparently only New Zealand manufactures and uses the herbicide 2,4,5-T in agriculture.[142] Some countries have also given up 2,4-D.[23] In some countries such as Japan the use of PCB is prohibited.[23] In others it is strictly controlled, ecologically safe replacements for these products are being developed.[142] Because of the change in composition of ethylated petrol the discharge of xenobiotics (III)–(VIII) when burning it in motor vehicles is reduced.[301] Ecologically safe methods (pyrolytic and others) of destroying chorine-containing vat residues are being developed.[532]

The second direction embraces *organisational measures* providing prevention and limitation of contamination of the environment by sudden discharges of xenobiotics. For example it is forbidden to use electric power equipment with PCB in large buildings in the USA to avoid contamination by PCB in fires,[23] which took place previously.[33,125]

The third direction of work concerns the *destruction of the results of dioxin contamination of territory*, the elimination of xenobiotics from the environment and from industrial waste and burial of the latter. Seemingly the first historically was the massive work on the decontamination of the vicinity of Seveso (Italy) from dioxin (I).[100] Similar measures were taken in the state of Missouri and in several other contaminated regions of the USA.[547,554] Expensive and very careful work has been accomplished in the industrially developed countries on the destruction of previously manufactured dioxin products such as residues of the herbicide 'Agent Orange' (USA),[310] PCB (Japan),[23] etc. Necessary measures are being applied in relation to the decontamination of large dumps which proved in fact to be sources of xenobiotics (III) and (IV) (Netherlands,[313,314] USA,[547,554] etc.).

Achievements in the area of low temperature and thermal methods of dehalogenation and destruction of xenobiotics (III)–(VIII) have been summarised.[211,532,554–556] The most effective are considered to be the destruction of dioxins by catalytic oxidation and by photodestruction, after preliminary recovery from soil with solvents and sublimation in solution at 500–600 °C. Recently biological methods of decomposing dioxins have been developed. For example fungi of certain species have been isolated which are capable of decomposing xenobiotics (III) and (IV) to nontoxic products.[557] They may find use for the partial decontamination of highly dangerous vat residues if the rate of biodestruction of dioxins by these organisms can be appreciably increased. It has been shown possible to decontaminate water contaminated with dioxins by ozonisation.[558]

Numerous procedures for the decontamination of soil and of chemical industry waste products from xenobiotics are being developed in the USA.[532,554,555] Mobile equipment has been devised for the thermal treatment of soil contaminated with xenobiotics and of solid and liquid waste at temperatures up to 4500 °C. Xenobiotics are more than 99.9999% destroyed by this.[554] A drawback of this procedure is the low throughput and high energy cost so preliminary recovery and destruction of dioxins by other methods is considered expedient. The dechlorination of xenobiotics found in waste and extracted from contaminated soil in laboratory and field conditions has been worked out by melting them with ethyleneglycol, with solid KOH or other alkalis.[559,560] Burial of soil contaminated with xenobiotics in abandoned mine workings has been proposed.[554] Special clays have been proposed for the efficient recovery of highly toxic xenobiotics (III) and (IV) from industrial waste.[532,561,562] Stabilisation procedures, including consolidation of xenobiotics in industrial waste products (such as by vitrification), have been developed.[532]

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In any event the global attempt to study the problem is thriving. Some developed countries have learned from their technological errors, others have learned from abroad. Our society must not be out of the picture while experiencing a period of brisk ecologisation. First of all this must be directed towards acceptance of exhaustive measures for the exclusion of dioxins from the environment and particularly from foodstuffs. The organisation of All-Union chemical and toxicological monitoring for this technological danger and, which is very difficult, the fitting out of our existing analytical centres of various types with appropriate instruments are also important. Finally data on the content of dioxins in the discharges from all our undertakings and in their dumps must remain an obligatory element of their technological passports.[563]

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