ORGANOCHLORINE COMPOUNDS IN THE GENERAL POPULATION OF THE SEVENTIES AND SOME OF THEIR BIOLOGICAL EFFECTS (IN MAN AND ANIMALS)

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ABSTRACT

The interaction of an organism and its environment is determined, to a significant degree, by the composition of the environment and the biochemical individuality of the given organism.

A characteristic of the living organism is to carry the foreign compounds which enter them through continuous cycles of activity like their own constituents. Some of the compounds of the environment accumulate to some extent in the animal body. This storage constitutes a dynamic process.

At a certain storage level, effects on the metabolism of normal constituents of the animal body, on the genetical make-up, and on its defence mechanisms (detoxication processes, neuro-endocrine, and immunologic processes) are observed.

This paper reports on the size of Organochlorine Insecticides and Polychlorinated Biphenyls storage in the human general population in the seventies and some of the biological effects of these compounds on humans and experimental animals.

Multicellular organisms have to offer their cells an environment similar to the marine environment of unicellular organisms to which they no longer have free access. The complexity of the developed animal body is to a large extent the result of the need for maintaining the characteristics of the internal environment in a balanced state, in spite of the influence of the ever-changing external environment on which the organism is strongly dependent.

Homeostatic processes permit recovery after each displacement from the optimal state of the internal environment. Many homeostatic processes are still poorly understood.

A homeostatic process is made up of two opposing mechanisms which tend to maintain a given parameter of the internal environment. The degree of complexity in a homeostatic system is proportional to its importance for survival. In maintaining homeostasis of an essential parameter of the internal environment, a new level of activity of the organs involved as effectors of

this homeostatic process is required. Thus, while one system is being stabilized, it is done at the expense of the activity of another system.

Many environmental pollutants enter the internal milieu of the animal body which reacts to xenobiotics by initiating a series of enzymatic and immunological processes aimed at inactivating and/or withdrawing them. It reacts also to their biological effects by mechanisms of homeostasis which strive to reestablish the status quo ante.

The faculty of an organism to rid itself of xenobiotics or of their biological effects is a function of its genetic equipment and of the extent to which this equipment has been used during the course of its life (i.e. the phenotype acquired by cultivation of the adaptive inherited capacities of the organism) and represents defence or adaptive mechanisms.

If the quantity of a noxious agent reaches a certain level, due to its high concentration in the external environment or to the poor capability of the organism to get rid of it, or if certain homeostatic processes fail to maintain the level of a disturbed parameter of the internal milieu, acute or chronic toxicity or chronic biological effects may arise.

Diseases may also appear indirectly as a result of adaptive mechanisms since adaptive non-specific biochemical processes may quantitatively affect compounds naturally occurring in the animal body with important roles in physiology.

It follows that there is a need to establish the MAC of xenobiotics and also to establish which parameters of the internal environment are affected by specific xenobiotics. Suitable preventive programmes regarding man and environment should be elaborated.

A large number of synthetic compounds have become current constituents of the external environment in recent decades[138]. At the same time, many natural components of the soil have been brought in ever-increasing quantities to the surface by man's activity (mining and agriculture).

For a long time, investigators in environmental and medical sciences have striven to establish criteria for the allowable level of environmental hazards which would enable the human body to maintain its homeostases both in living and industrial environments. Concepts, methods and findings in physiology, pharmacology, biochemistry and epidemiology have succeeded in providing some level of confidence for biologists and physicians that our epoch is able to put the achievements of technology into practice, improving economic welfare without harm to the health and survival of mankind. This mood of confidence was characteristic of the end of the fifth decade and has been expressed in the debates and recommendations of several international meetings. The last two decades, however, have cast their shadows on this confidence, and findings have been brought to light which seem to be controversial, raise concern and require careful consideration.

The reasons which led to these conjectures include:

— the rich flow of chemicals and drugs which penetrated the living and working milieu at a rate beyond the capacity of scientific supervision to monitor in all its biological implications.

— the extraordinary development of chemistry and biology which has helped us to understand the large spectrum of individual behaviour towards environmental hazards in presumably healthy people.

As a corollary of this stage in the development of our civilization, it becomes important to know what sort of components of the contemporary environment enter the animal body, to what extent they affect biochemical processes, and in which circumstances we consider as 'allowable' their concentration in man's tissues. Most of the new compounds are constituents also of the non-occupational environment. It therefore becomes important to establish the concentration of such chemicals in the body of presumably healthy people, not occupationally exposed.

This point of view appears quite integrated into the conception of modern public health, which speaks nowadays in terms of 'chemical epidemiology'[35]. But the crystallization of this concept has taken about two decades and DDT constituted the 'guinea-pig' of a controversial evolution in biological thinking which seems far from nearing its end.

The epidemiological approach to assessing man's exposure to environmental trace substances includes:

(a) the assessment of the internal chemical load constituted by trace substances as such (e.g. metals, pesticides and other synthetic organic compounds);
(b) the measurement of biological responses induced by the internal chemical load. This refers to the impact on the metabolism of normal constituents of the human body and on the activity of defence systems;
(c) the exploration of a cytogenetic indicator, namely the occurrence of chromosomal abnormalities following environmental exposure to certain trace substances.

(a) In this paper, we refer to organochlorine compounds with special emphasis on DDT and its metabolites, BHC isomers, H. Epoxide, Dieldrin, HCB and PCBs which together represent a large percentage of OCC environmental pollution.

As pesticides or enhancers of the activity of some pesticides, these compounds are important to economy and preventive medicine. PCBs are not only used in the formulation of some chlorinated pesticides[66] but also have widespread industrial use due to certain unique properties. The use of OCI on a large scale began with DDT during the 1939–45 war. At that time, PCBs already had about 15 years of industrial use. None of these compounds was detected in the environment after a prior planning.

It was intuition that led Howell to suppose that DDT may be found in men exposed to this compound since he knew about its presence in the adipose tissue of sheep exposed to DDT in the fields. He reported in 1948, the presence of DDT in a lipoma removed from a 37 year old male worker from Oklahoma[67]. PCBs were detected, by chance, by Jensen in 1966, who identified, by mass spectroscopy, some peaks which appeared on the graph of gas-chromatographic assessment together with OCI peaks[69].

Beginning with the sixties, a large number of publications established the storage level of OCC in groups of the general population and in people occupationally exposed to these compounds.

The storage was assessed especially in the subcutaneous tissue of the anterior abdominal wall. With improvement of methodology, it became possible to assess OCC in plasma on the ng scale.

It must be said that the analytical procedure differs from laboratory to

laboratory and this may be looked upon as a handicap in the elaboration of a map of the distribution of OCC in the general population throughout the world. In some countries (USA and Israel) surveys were performed for many other countries, and at least for these studies, the analytical procedure parameter may not constitute a problem. Some laboratories have cross-checked some of their samples in order to match their technical procedure (our laboratory with the Atlanta Center, and other countries too).

Because of the very large range of values in the samples (between fractions of p.p.m. to tens of p.p.m.), a large number of samples had to be studied.

The question of whether plasma level of OCC may substitute for the adipose tissue storage gave rise to comparative studies, some authors claiming a direct correlation between adipose tissue and plasma levels[44] while others deny such a relationship[118].

In favour of the plasma OCC assessment, we may say that blood is easily obtainable in people occupationally exposed to OCC or in persons hospitalized for medical purposes. Moreover, blood levels represent the actual levels of OCC in the internal environment and therefore, are a better index of biological implications of OCC pollution. The plasma level rises with the intensity of exposure.

Another debated question was whether the storage level should be expressed by the concentration of OCC in the tissue as such or in its extracted lipids.

Because of the differences in the quantity of adipose tissue and in the proportion of lipids found in the adipose tissue of each person, the two possibilities give only an approximate reflection of the situation. The total body load may permit the appreciation of the hazard represented by OCC residues in special circumstances like starvation or sudden loss of weight resulting from disease. The assessment of the body load is unfortunately also an approximation.

All these problems indicate the need for a standardized approach in the analytical procedure of OCC assessment.

The importance of the assessment of OCC residues in man is proved by the need for adjusting preventive measures according to the geographical characteristics of OCI storage.

The map we intend to draw emphasizes the findings regarding only adipose tissue storage of OCC expressed in p.p.m. of whole tissue and the content of OCC (expressed in p.p.b.) in whole milk

We chose this presentation because a large number of publications report the OCC residues in this way. The content of OCC in whole milk (rather than the value of OCC in milk extracted lipids) may lead us to the assessment of the daily intake of OCC in breast-fed infants, which has proved to be a hazard in some areas.

As we see from the analysis of the following tables, OCI residues were analysed in groups of people on all the continents and were found to depend on several parameters, namely:

(1) The storage of OCC in man is a widespread phenomenon, in fact they are a current constituent of humans living in the second half of this century.

(2) The storage of OCC is proportional to the degree of exposure, since occupationally exposed people store the highest levels[146].

(3) The storage of OCI is higher in men, and there is a direct relation to age, starting with the intrauterine life up to the age of 45 years. In some countries (USA, Israel), this direct relationship exists for all the age groups, while in others a decrease in the storage level occurs after 45 years of age.

(4) The geographical location of the groups sampled seems to have an influence on OCI storage. The storage is higher in south and east Europe when compared with north and west Europe. The same applies when we compare Canada to the USA. The cause of these geographical differences may be local agriculture or sanitary practices.

(5) The physiological state of the body (e.g. pregnancy[110]), obesity, loss of weight, and pathological conditions like liver disease[99], carcinoma[115], seem to influence the storage level of OCC in opposite directions. [The milk of obese women contains lower amounts of OCI than that of women with normal weight (GFR, GDR[82])].

(6) Race also seems to influence the storage level. Davies[34] found higher concentration in negroes of the USA. In South Africa, a lower level of OCI storage was reported by us in non-white people[144]. It is possible that socio-economic conditions may explain such differences. In a study of OCI serum levels in a multiracial population, significant differences were found among the various ethnic groups: sera from Chinese contained the highest levels of *p,p'*-DDT and β-BHC. Koreans had the highest levels of Dieldrin, and people from triracial backgrounds had the highest levels of γ-BHC[81].

(7) There is a bidirectional relation between OCI and some drugs which influence their storage level by activation or inversely by inhibition of enzymatic systems involved in the metabolization of these compounds. Volunteers receiving diphenylhydantoin[36] as well as patients receiving phenobarbital and/or diphenylhydantoin[163] had a lower OCI storage level when compared to controls. In an OCI plant, one of the workers who took phenobarbital and diphenylhydantoin over 25 years for post traumatic epilepsy had no or trace amounts of DDT and DDE residues in his serum[85].

(8) The banning of special OCC which reached too high a level in special areas (e.g. β-BHC in Japan) led to decrease in storage of the banned compound (β-BHC in Japan decreased 20–50 per cent[102]).

(9) The exposure of the general population to OCI occurs especially from contaminated food but also from household use (β-BHC residue was higher in the milk of non-farm women in Japan[9, 127]). Mothers in non-agricultural families consume larger amounts of beef and milk daily, when compared to farm women[58].

(10) The greatest exposure of the general population, non-occupationally exposed to OCC, is that of infants fed by mother's milk. Mother's milk has a higher OCC residue than cow's milk and in some regions the exposure is high enough to cause biological effects (inhibition of corticoids synthesis, gluconeogenic enzyme activity, and the interference with calcium, vitamin D and sex hormone metabolism[7]). In Guatemala, OCI residue of mother's milk is 25–30 times the average level found in the USA, UK and Sweden (Löfroth[89]).

(b) Appreciation of the biological effects induced by the OCC body burden. The findings of OCC residues in men and the studies regarding the

Table 1. Storage of OCC in fat tissue of humans (p.p.m.). North America

Authors	Ref.	Country	T. DDT	BHC	Diel.	PCB	HCB	Year
Laug *et al.*	86	USA	5.3					1950
Hayes *et al.*	61	USA	11.7					1955
Dale and Quinby	33	USA	6.7	0.20	0.15			1961
Hoffman *et al.*	64	USA	10.3	0.57*	0.11			1964
Quinby *et al.*	114	USA	12.7					1961
Hoffman *et al.*	63	USA, Chicago	10.4	0.48*	0.14			1963
Hayes *et al.*	60	USA, New Orleans	10.3	0.60*	0.29			1965
Fiserova-Bergerova *et al.*	50	USA	10.6		0.22			1966
Zavon *et al.*	169	USA	7.6		0.31			1964
Shafer and Campbell	122	USA	2–31					1964
Edmundson *et al.*	43	USA, Florida			0.22			1965
Morgan and Roan	95	USA, Arizona	6.5		0.14			1967
Davies and Edmundson	34	USA, Florida	12.4					1966
Curley *et al.*	28	USA, Atlanta	8.8	0.55	0.24			1969
Warnick	162	USA, Utah	9.0		0.20			1968
			7.2		0.15			1969
			5.3		0.15			1970
Price and Velch	112	USA, Michigan				→2.0		1972
Jobs	70	USA				→2.0		1972
Biros and Walker	15	USA						1970
Durham *et al.*	40	USA, Alaska	3.0					1960
Cassaret *et al.*	24	USA, Hawaii	5.7					1968
Kadis *et al.*	74	Canada	4.3	1.07*	0.01			1967
Read and McKinley	116	Canada	4.9					1959
Ritcey *et al.*	117	Canada	4.8	0.01*	0.12			1969
Mastromatteo	93	Canada, Ontario	9.2		0.22			1970

* Only one isomer.

Table 2. Storage of OCC in fat tissue of humans (p.p.m.). South America

Authors	Ref.	Country	T. DDT	BHC	Diel.	PCB	HCB	Year
Wassermann *et al.*	147	Brazil	7.9	0.25*	0.13			1970
Wassermann *et al.*	142	Argentina	13.2	2.43	0.30			1969
Fernandez *et al.*	49	Argentina	6.6					1970
Astolfi *et al.*	10	Argentina	2·7–30.0					1970

* Only one isomer.

Table 3. Storage of OCC in fat tissue of humans (p.p.m.) Europe.

Authors	Ref.	Country	T. DDT	BHC	Diel.	PCB	HCB	Year
Abbott *et al.*	1	England	3.0	0.31	0.21			1966
Abbott *et al.*	2	England	2.5	0.29	0.16			1969
Robinson *et al.*	119	England	4.1*	0.01	0.21*			1964
Robinson *et al.*	118	England	4.0*		0.22*			1964
Hunter *et al.*	68	England	2.2*		0.21			1961
Egan *et al.*	45	England	3.3	0.42	0.26			1963
Cassidy *et al.*	25	England	2.6*					1965
Widmark and Jensen	166	Sweden	7.3					1967
Bjerk	16	Norway	3.2			0.85		1972
Weihe	164	Denmark	3.3	0.20	0.20			1966
Vlieger *et al.*	133	Holland	2.2		0.17			1968
Maier-Bode	92	Germany	2.3					1958
Engst *et al.*	47	Germany, DDR	13.1‡					1966
Engst and Knoll	46	Germany, DDR				6.40‡	5.40‡	1971
Wüncher and Acker	168	Germany	4.1	0.56	0.18			1967
Acker and Schulte	4	Germany, Münster	3.8	0.50		5.70	6.30	1971
Borneff	18	Germany	5.0					1971
Barchet	12	Germany, Neckar	4.9					1972
Hayes *et al.*	59	France	5.2					1963
Fournier	51	France	5.3	0.15				1969
Fournier *et al.*	52	France	3.3	0.10	0.40			1971
Jonezyk and Bojanovska	72	Poland	2–10.0					1968
Juszkiewisz and Stecy	73	Poland	12.4	0.13				1971

Ochynski and Bronicz	104	Poland	16.0				1972
Bogusz,	17	Poland	11.9				1972
Trojanowska *et al.*	129	Poland	12.4				1972
Vaskovskay and Komarova	132	USSR	8.4				1967
Gracheva	55	USSR	0–50.0				1969
Halacka *et al.*	56	Czechoslovakia	9.2				1963
Rosival *et al.*	120	Czechoslovakia	20.3	9.78			1963
Denes	38	Hungary	12.4				1960
Denes and Tarjan	39	Hungary	24.1				1963
			13.8				1966
Berend *et al.*	13	Hungary	13.1	2.30			1969
Soos *et al.*	123	Hungary	18.9	0.76			1970
Pesendorfer *et al.*	109	Austria, Vienna	6.3	1.90	0.10	3.50	1973
Adamović *et al.*	6	Serbia	11.5	0.14	0.09		1970
Aizicovici *et al.*	8	Roumania	21.7				1965
Mandroiu and Jordachescu	91	Roumania, Vrancea		0.08–42.0			1971
Kaloyanova	75	Bulgaria	10.0	0.76			1972
Kanitz and Castello	77	Italy	5.0				1965
Delvechio and Leoni	37	Italy	15.5		0.68		1966
Pacagnella *et al.*	108	Italy	10.8	2.25	0.84		1963
Prati *et al.*	111	Italy	9.3		0.07		1966
Llinares and Wasserman	88	Spain	14.8				1966
Abbott *et al.*	1	England	0.8†	0.14	0.09		1966
Engst *et al.*	48	Germany, DDR	2.4†				1967
Unterman *et al.*	131	Roumania	4.8†				1970

* Geometric means.
† In stillborn and first days of life.
‡ On a fat basis.

Table 4. Storage OCC in fat tissue of humans (p.p.m.). Asia

Authors	Ref.	Country	T. DDT	BHC	Diel.	PCBs	HCB	Year
Dale *et al.*	32	India	12–31	0.86 −1.7	0.03 -0.06			1965
Wassermann *et al.*	137	Israel	19.2					1963
Wassermann *et al.*	139	Israel	15.4					1965
Wassermann *et al.*	161	Israel	14.4	0.47	0.12			1969
Wassermann *et al.*	156	Israel				2.75		1973
Mughal and Rahman	96	Pakistan	25.0					1973
Wassermann *et al.*	151	Thailand	13.0					1970
Nishimoto *et al.*	101	Japan, Kochi	6.9	12.2	0.46			1970
Mizutani *et al.*	94	Japan, Kyoto	9.7	11.7	0.19	4.7		1972
Doguchi *et al.*	31	Japan, Tokyo	3.7	3.2	0.33			1972
Curley *et al.*	28	Japan	2.5	1.5	0.13		0.08	1969
Ui	130	Japan				5.0		1972
Curley *et al.*	27	Japan				0.8		1973
Kasai	78	Japan	8.1	4.3				1972
Suzuki *et al.*	124	Japan, Hiraga	4.5	2.4	0.16			1970
			2.1	3.0	0.21			1971
			4.0	4.0	0.43			1972
Tatsumi *et al.*	126		4.2	2.4	0.16			1971
Kawanishi *et al.*	80	Japan, Usaga	6.4	2.7	0.13			1973

Table 5. Storage of OCC in fat tissue of humans (p.p.m.). Oceania

Authors	Ref.	Country	T. DDT	BHC	Diel.	PCBs	HCB	Year
Bick	14	Australia	1.8*		0.05*			1965
Wassermann *et al.*	140	Australia	9.4	0.68	0.67			1968
Lugg	90	Australia	3.1		0.21			1969
Brody and Siyali	20	Australia					1.25	1972
Brewer and Grath	19	New Zealand	5.8		0.27			1966
Darcre	30	New Zealand		0.50				1963
Copplestone *et al.*	26	New Zealand	5.4		0.41			1965
			3.9		0.27			1969
Dyment *et al.*	42	New Guinea				0.0		1971

* Geometric mean.

Table 6. Storage of OCC in fat tissue of humans (p.p.m.) Africa.

Authors	Ref.	Country	T. DDT	BHC	Diel.	PCBs	HCB	Year
Wassermann *et al.*	144	South Africa	6.38	2.41	0.04			1969
Wassermann *et al.*	141	Nigeria	8.75	0.68	0.22			1967
Wassermann *et al.*	152	Nigeria	6.50	0.30	0.18			1970
Wassermann *et al.*	150	Kenya	4.60	0.29	0.10			1970
Wassermann *et al.*	160	Uganda	2.90	0.08	0.04			1970

Table 7. OCC residues in mother's whole milk (p.p.b.)

Authors	Ref.	Country	T. DDT	BHC	Diel.	PCBs	HCB	Year
Bjerk	16	Norway	50–100					1972
Westöö and Norén	165	Sweden	113.0					1968
Egan *et al.*	45	England	130.0	13.0	6.0			1965
Knoll and Iayaraman	82	Germany	320.0					1971
Acker and Schulte	3	Germany	112.0	18.0		103.0	153.0	1971
Engst and Knoll	46	Germany	230.0					1970
Kontek *et al.*	84	Poland	280.0					1971
Bogusz	17	Poland	715.6					1972
Gracheva	55	USSR	0–1000					1964
Komarova	83	USSR, Urban	100.0					1970
Komarova	83	USSR, Rural	190.0					1970
Mándroiu and Jordáchescu	91	Romania, Vrancea		0–560.0				1971
Adamović *et al.*	5	Serbia	207.5	5.0				1969
Adamović *et al.*	7	Serbia	587.1	14.0	79.0			1972
Laug *et al.*	86	USA, Black	130.0					1951
Quinby *et al.*	113	USA	145.0					1965
Curley and Kimbrough	29	USA	70.0	7.0	6.0			1967
Wilson *et al.*	167	USA, White	170.0					1973
Savage *et al.*	121	USA	7–495.0	0–38.0	0–11.0	40.0 →100.0		1971
Lofröth	89	Central America	3100.0					1971
Olszyna Marzys *et al.*	105	Guatemala	2863.3	0–100.0				1973

Lugg	90	Australia	170.0	2.0	15.0	75.0	1969
Newton and Greene	100	Australia	142.0			52.5	1970
Hornabrook *et al.*	65	New Guinea	29.0–95.9				1972
Gejvall *et al.*	54	Ghana	29.0	30.0		< 5.0	86.0 1972
Takeshita and Inuyama	125	Japan, Agric.	79.0	142.9	0–12.0		1970
Takeshita and Iniyama	125	Japan, Nonagr.	66.0	250.9	0–43.0		1970
Kato *et al.*	79	Japan	19–105.0	18–740	0–12.0		1971
Oura *et al.*	107	Japan	33.0	49.0		30.0	1972
Anon.	9	Japan	60.2	115.4		3.4	1971
Anon.	9	Japan	56.2	96.0		3.1	1972
Narafu	98	Japan		20–400.0			1970
Hidaka *et al.*	62	Japan	95.0	120.0	5.0	50.0	1972
Tattori Res. Hyg. Inst.	128	Japan	124.0	109.3	4.7		1972
Kamata	76	Japan	90–180.0	70–160			1972
Osaka Pref.	106	Japan	21.0	161.5	1.0		1971
Osaka Pref.	106	Japan	43.0	180.0	2.0		1972
Hayashi	58	Japan, Agric.	56.3	92.6	3.7		1971
Hayashi	58	Japan, Nonagr.	63.5	143.4			1971
Nishimoto *et al.*	103	Japan				30.0	1971
Nagai	97	Japan, Oshima	20.0	163.0			1972
Nagai	97	Japan, Nagato	31.0	219.0			1972
Nagai	97	Japan, Yanai	12.0	94.0			1972
Nagai	97	Japan, Assa	33.0	247.0			1972

metabolism of these compounds have opened the way to epidemiological toxicology and ecology and thrown new light on the understanding of the defence mechanisms of the animal body against xenobiotics.

These findings have helped us to understand the unwanted effect on species which could not adapt to the presence of OCC in their environment and became victims of the 'natural' selection produced by the new parameters of the environment.

Very interesting biological activities of OCC were found after the discovery by Hart and Fouts that DDT 'shorted' the half-life of a drug by interfering with enzymatic activity of drug detoxication[57]. This discovery, which was made by chance, had a tremendous influence on biological thinking in general with important repercussions in pharmacology and medicine on the one hand and on the attitude towards OCC environmental pollution on the other. Soon enough, the interaction between OCC metabolism and that of some naturally occurring compounds in the human body was reported.

The problem is no longer that of storage in the animal body of inert compounds which have the annoying defect of being remanent, but the storage of active compounds which interfere with the metabolism of foreign as well as naturally occurring compounds in the animal body and do so at the minute levels detected by advanced chemical procedures.

As far as the biological effects of OCC are concerned, we undertook the study of serum cholesterol and serum PBI in workers occupationally and naturally exposed to OCI[145,148] and in animals fed extra dosages of OCC.

The study of cholesterol homeostasis was suggested by the inducing of Smooth Surfaced Endoplasmic Reticulum (SSER) proliferation by OCI and other organochlorine compounds like Polychlorinated Biphenyls (SSER probably being the site of cholesterol synthesis). Serum cholesterol was found within the range considered as normal. However, in the over 45 year age group, a statistically significant increase was found when occupationally and non-occupationally exposed workers were compared. We thought that OCI induced an increase of cholesterol synthesis, a process which was masked by a concomitant breakdown. In the over 45 year age group, a diminished reactivity of homeostatic processes may explain the findings of enhanced cholesterol synthesis which is less masked by concomitant catabolism.

The study of serum PBI was initiated by us in people occupationally exposed to OCI and in animals fed a diet containing *p,p'*-DDD, Dieldrin, γ-BHC, or PCBs, because of the possibility of competition for plasma thyroxine binding globulin between OCC and thyroxine owing to the resemblance in chemical structure of these compounds.

Serum PBI was significantly lower in workers occupationally exposed to OCI when compared to non-occupationally exposed workers[148]. The euthyroid clinical state of people occupationally exposed to pesticides suggests that even if the presence of OCI in the animal body affects the metabolism of thyroxine, thyroxine homeostasis is maintained by a sustained effort of the hypophyso-thyroid system.

PBI serum levels were also significantly decreased in OCI (Dieldrin or γ-BHC) receiving rabbits[154] as well as in rats with subacute exposure to PCBs[157,158]. These data confirm the findings we described in people

occupationally exposed to OCI, and underline a common biological effect of the two groups of OCC (OCI and PCBs).

This action of OCC (OCI and PCBs) on the thyroid gland was better understood following ultrastructural research[157] which showed features of hyperfunction[157] (and unpublished data regarding *p,p'*-DDT and Dieldrin). A more rapid degradation of thyroid hormones in the presence of a high level of OCC (which are powerful inducers of non-specific metabolizing enzymes) resulted in morphological features of hyperactivity in the thyroid gland due to a negative feedback reaction.

Following the line of defence of the animal body against environmental hazards, we studied the effect of OCC on the immunological response to antigens[143,149].

Rabbits had an impaired immunological response to soluble and particulate antigens when they received 200 p.p.m., *p,p'*-DDT in their drinking water. Total gamma globulins decreased at the expense of the 7S fraction. The antibody titre to ovalbumin[143] *Salmonella typhi* and Sheep Red Blood Cells (SRBC)[149] also decreased. The impairment of these immunological indices was higher in the *p,p'*-DDT–*Salmonella* receiving rabbits than in the *p,p'*-DDT–SRBC receiving rabbits.

The plasma total DDT level differed significantly in the two groups receiving *p,p'*-DDT (*p,p'*-DDT–*Salmonella* and *p,p'*-DDT–SRBC receiving rabbits). This finding may explain the different degree of impairment of the immunologic response, the higher plasma DDT level having a more marked effect. These differences in total DDT plasma level in the two groups of rabbits which received the same amounts of *p,p'*-DDT in their drinking water may be considered as a consequence of the concomitant presence of a different kind of foreign antigen in the internal milieu[149].

A bi-directional relationship between a detoxication process and an immunological response to antigens was suggested by these findings.

Dieldrin and γ-BHC inhibited the tendency of the 7S fraction of serum gamma globulins to increase after *Salmonella typhi* administration[154].

In rabbits receiving *p,p'*-DDT, Dieldrin and/or PCBs-1221 there was a tendency towards a decrease in the level of gamma globulin fractions (IgG and IgM) which was statistically significant for Dieldrin and PCBs[158].

Recently a lowering of gamma globulin fraction of serum proteins was noted in guinea-pigs fed 10 p.p.m. PCBs-1254[136].

Thymus atrophy and lymphopenia in PCBs receiving rabbits[135] and increased mortality from hepatitis virus in ducklings receiving PCBs[53] have also been described.

Ehrlich ascites tumour cells were inoculated (2×10^6) i.p. to normal and *p,p'*-DDT receiving mice. A week after deaths began to occur, 24 per cent of the rats which received *p,p'*DDT and 76 per cent of the contol rats were still alive (unpublished data).

The serum albumin level rose in rabbits receiving OCI and fell in those receiving PCBs[158]. PCBs acted in the same way as OCI in lowering the serum gamma globulin levels and in opposite ways on serum albumin levels. An interpretation of these dissimilar features of OCI and PCBs was possibly due to the investigation of the effect of *p,p'*-DDT and PCBs on the hypophyso-adrenal axis.

It is considered that *p,p'*-DDT has no effect on the hypophyso-adrenal axis, an inhibitory effect being attributed to *o,p'*-DDD. Yet the hypertrophy of adrenal glands in rats undergoing surgical trauma was smaller in rats receiving *p,p'*-DDT when compared to normally fed rats[143] which raised the problem of the influence of *p,p'*-DDT on the chain of biochemical events in the adaptation of zona fasciculata activity to the needs of the organism[155]. This finding suggests that *p,p'*-DDT has a certain inhibitory influence on the hypophyso-adrenal axis.

In rats receiving PCBs (1221 and 1254) we found morphological features in the zona fasciculata of the adrenal gland indicating increased morphological activity[153]. These findings conformed with physiological features of adrenal zona fasciculata hyperfunction (statistically significant increase of plasma corticosterone in male and female rats receiving PCBs in their diet[159]). The results were interpreted as evidence of the need for higher levels of corticosteroids in defence against the stressor character of PCBs and perhaps also of the need for catatoxic activity of corticosteroids.

The opposite effects of OCI and PCBs on the adrenal gland may explain the respectively anabolic and catabolic action of these compounds on serum albumin.

(c) The exploration of the genetic hazard following exposure to trace substances should become an integral part of toxicological control of the environment.

Only during the 1939–45 war did it become clear that chemicals may induce mutations when Auerbach and Robson described their observations on the mutagenic effect of nitrogen mustard[11]. Since then, many chemical compounds have been shown to be mutagenic in lower organisms as well as in mammals and man.

Recent publications show a significant increase in mutation rates induced by DDD in mice[23]. DDT and DDA are considered possible mutagens in *Salmonella typhimurium*[22], in *Drosophyla melanogaster*[134], in mice[71] and in rats[87]. Bone marrow cultures in Mallard ducks exposed to Dieldrin showed an increase in chromosomal structural alterations[21].

Mutagenesis is a dose-related biological effect[41]. The estimation of safe levels of OCC has to be performed as for radiation-induced mutations. Most publications refer to findings in submammalian and mammalian systems using different tests. Due to the lack of data for man, a safety factor has to be calculated from animal experiment findings, although this safe level may prove inadequate in the future, when more data are available.

Improvement in the knowledge of chemical mutagenesis in man may result from:

(1) Follow-up of fluctuation in the mutation frequency in stable human populations in order to detect changes in the occurrence of genetic abnormalities. From this point of view, factories, plants and industrial areas may be considered laboratories in which possible genetic hazards can be followed since the industrial environment contains high concentrations of specific chemical compounds.

(2) Screening for chromosome abnormalities in leukocytes obtained from personnel occupationally exposed to OCC and for OCC plasma levels, may give important indications about dose–effect relationships since occupation-

ally exposed people store a higher level when compared to non-occupationally exposed people.

It has to be stressed that only a statistically significant increase in aberration rates in large groups of people can be considered as an indication of the mutagenic effects of a certain environment.

REFERENCES

[1] D. C. Abbott, R. Goulding and Y. O'G. Tatton, *Brit. Med. J.* **3**, 146 (1968).
[2] D. C. Abbott, C. B. Collins and R. Goulding, *Brit. Med. J.* **11**, 553 (1972).
[3] L. Acker and E. Schulte, *Ernährungsforschung*, **16**, 559 (1971).
[4] L. Acker and E. Schulte, *Umschau*, **71**, 848 (1971).
[5] V. M. Adamović, M. Hus and V. Djukić, in *2nd Yugoslav-Symp. Pest., Zagreb* (1969).
[6] V. M. Adamović *et al. Hrana i Ishrana*, **11**, 12 (1970).
[7] V. M. Adamović, B. Sokic and O. Petrovic, *Ernährungsforschung*, **16**, 579 (1971).
[8] H. Azicovici *et al. Trav. Sci. Inst. Hyg, Iassy*, p 142 (1960–1966).
[9] Anon. *Pestic. Business*, **56**, 458 (1972).
[10] E. Astolfi *et al. Arch. Argent. Pediat.* **68**, 20 (1970).
[11] C. Auerbach and J. M. Robson, *Nature, London*, **154**, 81 (1944).
[12] R. Barchet *et al. Dtsch. Lebensm.-Rundschau*, **68**, 69 (1972).
[13] E. Berend, I. Keeskemeti and G. Koppa, *Egészségtudomány*, **14**, 388 (1970).
[14] Marjorie Bick, *Med. J. Austral.* 1127 (1967).
[15] F. J. Biros and A. C. Walker, *Bull. Environ. Contam. Toxicol.* **5**, 317 (1970).
[16] J. E. Bjerk, *Tidssker. Norske Laegeforen.* **92**, 15 (1972).
[17] M. Bogusz, *Pol. Tyg. Lek.* **27**, 637 (1972).
[18] J. Borneff, *Zentralbl. Bakteriol. Hyg.*, I Abt., Orig. B, **155**, 220 (1971).
[19] H. V. Brewerton and H. J. W. McGrath, *NZ Jl Sci.* **10**, 486 (1967).
[20] M. N. Brody and D. S. Siyali, *Med. J. Austral.* **1**, 158 (1972).
[21] T. D. Bunch, *Diss. Abstr. Int.* **33**, 3381B (1973).
[22] W. Buselmaier, G. Roehrborn and P. Propping, *Bio. Zentralbl.* **91**, 311 (1972).
[23] W. Buselmaier, G. Roehrborn and P. Propping, *Mutat. Res.* **21**, 25 (1973).
[24] L. J. Casarett *et al. Arch. Environm. Health*, **17**, 306 (1968).
[25] W. Cassidy *et al. Mon. Bull. Min Health Lab. Serv.* **26**, 2 (1967).
[26] J. F. Copplestone, J. N. Hunnego and D. L. Harrison, *ZN Jl Sci.* **16**, 27 (1973).
[27] A. Curley *et al. Nature, Lond*, **242**, 338 (1973).
[28] A. Curley, M. F. Copeland and R. Kimbrough, *Arch. Environm. Health*, **19**, 628 (1969).
[29] A. Curley and R. Kimbrough, *Arch. Environm. Health*, **18**, 156 (1969).
[30] J. C. Dacre, *Proc. U. Otago Med. School*, **47**, 74 (1969).
[31] M. Doguchi *et al. Annu. Rep. Tokyo Metrop. Res. Lab. Pub. Health*, **22**, 131 (1971).
[32] W. E. Dale, M. F. Copeland and W. J. Hayes Jr, *Bull. World Health Org.* **33**, 471 (1965).
[33] W. E. Dale and G. E. Quinby, *Science*, **142**, 593 (1963).
[34] J. E. Davies and W. F. Edmundson in: *Epidemiology of DDT*, pp 39–48, Edited by J. E. Davies and W. F. Edmundson (1972)
[35] J. E. Davies, W. F. Edmundson and H. F. Kraybill, *Clin. Toxic.* **2**, 435 (1969).
[36] J. E. Davies *et al. Fd Cosmet. Toxicol.* **9**, 413 (1971).
[37] V. Del Vecchio and V. Leoni, *Nuovi Ann. d'Ig. Microbiol.* **28**, 107 (1967).
[38] A. Dénes, *Die Nahr.* **6**, 48 (1962).
[39] A. Dénes and R. Tarján, *MTA V. Oszt.* **18**, 379 (1967).
[40] W. F. Durham *et al. Science*, **134**, 1880 (1961).
[41] W. F. Durham and Clara H. Williams, in *Pesticides and the Environment: A Continuing Controversy*, pp 307–334. Ed. W. B. Deichman, Intercontinental Medical Book Corp. (1973).
[42] P. G. Dyment *et al. Bull. Environm. Contam. Toxicol.* **6**, 532 (1971).
[43] W. F. Edmundson, J. E. Davies and W. Hull, *Pesticides Monit. J.* **2**, 86 (1968).
[44] W. F. Edmundson, J. E. Davies and C. Morgade, in *Epidemiology of DDT*, pp 99–108. Ed. J. E. Davies and W. F. Edmundson (1972).
[45] H. Egan *et al. Brit. Med. J.* **11**, 66 (1965).
[46] R. Engst and R. Knoll, *Ernährungsforschung*, **16**, 569 (1971).
[47] R. Engst, R. Knoll and B. Nickel, *Pharmazie*, **62**, 654 (1967).

[48] R. Engst, R. Knoll and B. Nickel, *Pharmazie*. **24**, 673 (1969).
[49] J. C. G. Fernandez, *Bol. Secc. Plaguicidas*, **2**, 1 (1970).
[50] V. Fiserova-Bergerova, J. L. Radomski, J. E. Davies and J. H. Davies, *Ind. Med. Swig.* **36**, 65 (1967).
[51] E. Fournier, *Cah. Nutr. Diet*, **6**, 31 (1971).
[52] E. Fournier *et al. J. Europ. Toxicol.* **1**, 11 (1972).
[53] M. Friend and D. O. Trainer, *Science*, **170**, 1314 (1970).
[54] T. Gejvall, S. Jensen and G. Lofröth, private communication (1972).
[55] G. V. Gracheva, *Zdorovia Naselen*, No. 1, 125 (1969).
[56] H. Halacka, J. Hakl and F. Vymetal, *Česk. Hy.* **10**, 188 (1965).
[57] L. G. Hart and J. R. Fouts, *Proc. Soc. Exp. Biol. Med.* **114**, 388 (1963).
[58] M. Hayashi, *Jap. J. Med. Ass.* **68**, 1281 (1972).
[59] W. J. Hayes Jr, W. E. Dale and R. Le Breton, *Nature, London*, **199**, 1189 (1963).
[60] W. J. Hayes Jr, W. E. Dale and V. W. Burse, *Life Sci.* **4**, 1611 (1965).
[61] W. J. Hayes Jr *et al. AMA Arch. Industr. Health*, **18**, 398 (1958).
[62] K. Hidaka, T. Ohe and K. Fujiwara, *Progr. Med.* **82**, 519 (1972).
[63] W. S. Hoffman, H. Adler and W. I. Fishbein, *Arch. Environm. Health*, **15**, 758 (1967).
[64] W. S. Hoffman, W. I. Fishbein and M. B. Andelman, *Arch. Environm. Health* **9**, 387 (1964).
[65] R. W. Hornabrook *et al. Med. J. Austral.* **25**, 1297 (1972).
[66] I. Hornstein and W. N. Sullivan, *J. Econ. Ent.* **46**, 937 (1953).
[67] D. E. Howell, *Proc. Okl. Acad. Sci.* **29**, 31 (1948).
[68] C. G. Hunter, J. Robinson and A. Richardson, *Brit. Med. J.* i, 221 (1963).
[69] S. Jensen, *New Sci.* **32**, 612 (1966).
[70] A. R. Jobs, *Environm. Health Perspect.* **1**, 79 (1972).
[71] G. A. Johnson and S. M. Yalal, *J. Heredity*, **64**, 7 (1973).
[72] H. Jonczyk and A. Bojanovska, *Biol. Inst. Ochr. Roślin*, **41**, 59 (1968).
[73] T. Juszkiewicz and J. Stee, *Polski Tygad. Lekar.* **26**, 462 (1971).
[74] V. W. Kadis, W. E. Breitkreitz and O. J. Johašson, *Canad. J Pub. Health*, **61**, 413 (1970).
[75] F. Kaloyanova, in *XVII Int. Congr. Occup. Hyg., Buenos Aires* (September 1972).
[76] T. Kamata, *Jap. J. Hyg.* **27**, 439 (1972).
[77] S. Kanitz and G. Castello, *Giornale Igiene Med. Prevent.* **1**, 7 (1966).
[78] A. Kagai, in *Fifth Int. Congr. Rural Med., Varna* (1972).
[79] K. Kato *et al. Annu. Rep. Kanagawa Prefect. Inst. Pub. Health*, **21**, 85 (1971).
[80] A. Kawanishi, S. Asanuma and S. Nakamura, *J. Jap. Ass. Rural. Med.* **22**, 278 (1973).
[81] H. W. Klemmer, M. N. Rashad and M. P. Mi, *Pesticides and the Environment: A Continuing Controversy*, pp 53–61. Environmental Protection Agency: Chamblee, Georgia (1973).
[82] W. Knoll and S. Jayaraman, *Z. Gesamte Hyg.* **19**, 43 (1973).
[83] L. I. Komarova, *Pediatr. Akusherstvo Hinekol.* **35**, 19 (1970).
[84] K. M. Konte *et al. Ped. Pol.* **44**, 183 (1971).
[85] D. S. Kwalick, *J. Amer. Med. Ass.* **215**, 120 (1971).
[86] E. P. Laug, F. M. Kunze and C. S. Prickett, *AMA Arch. Industr. Health*, **3**, 245 (1951).
[87] M. S. Legator *et al. Ann. NY Acad. Sci.* **160**, 344 (1969).
[88] V. M. Llinares and M. Wassermann, *Medicina y Seguridad del Trabajo*, **59**, 29 (1967).
[89] G. Lofröth, *Ecologist*, **1**, 8 (1971).
[90] R. Lugg, private communication (1970).
[91] V. Mândroiu and M. Jordăchescu, *Igiena*, **20**, 363 (1971).
[92] H. Maier-Bade, *Med. Expt.* **1**, 146 (1960).
[93] E. Mastromatteo, in *Conference on Epidemiology and Toxicology of Pesticides*. Amsterdam (1971).
[94] T. Mizutani, M. Matsumoto and K. Fujiwara, *Progr. Med.* **81**, 666 (1972).
[95] D. P. Morgan and C. C. Koan, *Arch. Environm. Health*, **20**, 452 (1970).
[96] H. A. Mughal and M. A. Rahman, *Arch. Environm. Health*, **27**, 396 (1973).
[97] I. Nagar, *Annu. Rep. Yamaguchi Prefect, Res. Inst. Pub. Health*, **14**, 93 (1972).
[98] T. Narafu, *J. Clin. Nutr.* **39**, 26 (1971).
[99] H. Nawa, *J. Okayama Med. Soc.* **85**, 47 (1973).
[100] K. G. Newton and N. C. Green, *Pestic. Monit. J.* **6**, 4 (1972).
[101] I. Nishimoto, M. Uyeta and S. Tave, *Progr. Med.* **73**, 275 (1970).
[102] T. Nishimoto *et al. Progr. Med.* **82**, 515 (1972).
[103] T. Nishimoto *et al. Progr. Med.* **82**, 974 (1972).

[104] J. Ochynski and H. Bronisz, *Bromatol. Chem. Toksikol.* **5**, 345 (1972).
[105] A. E. Olszyna Marzys *et al. Bol. Of. Sanit. Panamer.* **74**, 93 (1973).
[106] Osaka Prefect, The Countermeasures for damages due to agricultural pesticides, 2nd item of 1st clause of Chapter XII. A draft of the plan of Environmental Administration, pp 392–395 (1973).
[107] H. Oura *et al. J. Jap. Ass. Rural Med.* **21**, 300 (1972).
[108] B. Paccagnella, L. Prati and G. Cavazzini, *Nuovi Ann. d'Igiene, Microbiologia*, **18**, 17 (1967).
[109] H. Pesendorfer, I. Eichler and E. Glofke, *Wien. Klin. Wochenschr.* **85**, 218 (1973).
[110] Z. W. Polishuk *et al. Arch. Environm. Health*, **20**, 215 (1970).
[111] L. Prati, R. Pavanello and F. Ghezzo, *Bull. World Health Org.* **46**, 362 (1972).
[112] H. A. Price and R. L. Welch, *Environm. Health Perspect*, **1**, 73 (1972).
[113] G. E. Quinby, J. F. Armstrong and W. F. Durham, *Nature, London*, **207**, 726 (1965).
[114] G. E. Quinby *et al. J. Amer. Med. Ass.* **191**, 175 (1965).
[115] J. L. Rodomski *et al. Food Cosmet. Toxicol*, **6**, 209 (1968).
[116] S. T. Read and W. P. McKinley, *Arch. Environm. Health*, **3**, 209 (1961).
[117] W. R. Ritcey, G. Savary and K. H. McCully, *Canad. J. Pub. Health*, **64**, 380 (1973).
[118] J. Robinson and C. G. Hunter, *Arch. Environm. Health*, **13**, 558 (1966).
[119] J. Robinson *et al. Brit. J. Industr. Med.* **22**, 220 (1965).
[120] L. Rosival *et al.* in *Proceedings 4th Int. Congr. Rural Med., Usuda*, pp 40–42. Japanese Association of Rural Medicine: Tokyo (1969).
[121] E. P. Savage *et al. Pestic. Monit. J.* **7**, 1 (1973).
[122] M. L. Schaffer and J. E. Campbell, *Advanc. Chem. Ser. No. 60*, pp 89–98. American Chemical Society: Washington, DC (1966).
[123] K. Soos, V. Celeszky and R. Tarján, *Egészségtudomány*, **16**, 70 (1972).
[124] Y. Suzuki, H. Sugaya and S. Sasaki, *J. Jap. Ass. Rural Med.* **22**, 276 (1973).
[125] T. Takeshita and Y. Inuyama, *Annu. Rep. Shimane Prefect. Inst. Pub. Health*, **12**, 27 (1970).
[126] M. Tatsumi *et al.* in Fifth International Congress on Rural Medicine, Varna (1972).
[127] K. Tokutsu, T. Koyama and T. Yokoyama, *Annu. Rep. Wakayama Prefect. Inst. Pub. Health*, **19**, 59 (1972).
[128] *Tottori Prefect. Hyg. Res. Inst. Rep.* **12**, 22 (1972).
[129] M. Trojaroska *et al. Forensic Sci.* **1**, 239 (1972).
[130] J. Ui, *Laekartidningen*, **69**, 2789 (1972).
[131] W. H. Unterman, C. Gavrilescu and I. Chisel, *Igiena*, **19**, 69 (1970).
[132] M. F. Vaskovskaya and L. I. Komarova, *Sci. Conf. Young Sci., Kiev* (1965).
[133] M. Vlieger *et al. Arch. Environm. Health*, **17**, 759 (1968).
[134] E. Vogel, *Mutat. Res.* **16**, 157 (1972).
[135] J. G. Vos and R. B. Beems, *Toxic. Appl. Pharmacol.* **19**, 616 (1971).
[136] J. G. Vos and Th. de Roij, *Toxic. Appl. Pharmacol.* **21**, 549 (1972).
[137] M. Wassermann *et al. Arch. Environm. Health*, **11**, 375 (1965).
[138] M. Wassermann and D. Wassermann, 15th Int. Congr. Occup. Health, Vienna, *Abstracts*, Part 2, **6** (2), 954 (1966).
[139] M. Wassermann *et al. Pestic. Monit. J.* **1**, 15 (1967).
[140] M. Wassermann *et al. Industr. Med. Surg.* **37**, 295 (1968).
[141] M. Wassermann *et al. Proc. Lagos Int. Seminar Occup. Health for Developing Countries* (1968).
[142] M. Wassermann *et al. La Semana Medica*, **16**, 459 (1969).
[143] M. Wassermann *et al. Ann. NY Acad. Sci.: Biological Effects of Pesticides*, **160**, 393 (1969).
[144] M. Wassermann *et al. SA Med. J.* 646 (1970).
[145] M. Wassermann *et al. Bull. Environm. Contam. Toxicol.* **5**, 368 (1970).
[146] M. Wassermann, D. Wassermann and I. Ivriani, *Pestic. Symp. Fla*, 311 (1970).
[147] M. Wassermann *et al. Industr. Med.* **41**, 22 (1972).
[148] D. Wassermann *et al. Bull. Environm. Contam. Toxicol.* **6**, 85 (1971).
[149] M. Wassermann *et al. Bull. Environmn. Contam. Toxicol.* **6**, 426 (1971).
[150] M. Wassermann *et al. Ann. Soc. Belg. Méd. Trop.* **52**, 509 (1972).
[151] M. Wassermann *et al. SE Asian J. Trop. Med. Pub. Health*, **3**, 280 (1972).
[152] M. Wassermann *et al. Environm. Physiol. Biochem.* **2**, 59 (1972).
[153] D. Wassermann and M. Wassermann, *Proc. 17th Int. Congr. Occup. Health, Buenos Aires*, in press (1972).
[154] M. Wassermann *et al. Bull. Environm. Contam. Toxicol.* **8**, 177 (1972).

[155] D. Wassermann and M. Wassermann, *Environ. Physiol. Biochem.* **3**, 274 (1973).
[156] D. Wassermann, M. Wassermann and S. Cucos, *1st Asian Congr. Rural Med.* (November 1973).
[157] D. Wassermann *et al. 8th Inter-American Conf. Toxic. Occup. Med.* (8–11 July 1973).
[158] M. Wassermann *et al. Bull. Environm. Contam. Toxicol.* **10**, 42 (1973).
[159] D. Wassermann *et al. Environm. Res.* **6**, 334 (1973).
[160] M. Wassermann *et al. Bull. Environm. Contam. Toxicol*, **12**, 501 (1974).
[161] M. Wassermann *et al. Pestic. Monit. J.* **8**, 1 (1974).
[162] S. L. Warnick, *Pestic. Monit. J* **6**, 9 (1972).
[163] M. Watson, J. Gabica and W. W. Benson, *Clin. Pharm. Therap.* **13**, 186 (1972).
[164] M. Weihe, *Ugeskr. Loeg.* **128**, 881 (1966).
[165] G. Westöö and K. Noren, Nordforsk. Biocid-information, **14**, 6 (1968).
[166] G. Widmark and S. Jensen, *Miljövardsforskning Statens Offentliga Utregningar, Stockholm*, **43**, 171 (1967).
[167] D. J. Wilson *et al. Amer. J. Dis. Child.* **125**, 814 (1973).
[168] K. Wüncher and L. Acker, *Med. Ernährung*, **10**, 5 (1969).
[169] M. R. Zavon, C. H. Hine and D. K. Parker, *J. Amer. Med. Ass.* **193**, 837 (1965).