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COMMISSION ON TERMINAL PESTICIDE RESIDUES

IUPAC Reports on Pesticides (7)

TOXAPHENE (CAMPHETHLOR). A SPECIAL REPORT

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Commission on Terminal
Pesticide Residues (IUPAC)

T O X A P H E N E (Camphechlor)

A Special Report

Commission on Terminal Pesticide Residues

International Union of Pure and Applied Chemistry

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The report was presented at the Meeting of the Commission on Terminal Pesticide Residues at Deidesheim, Federal Republic of Germany, July 17-22nd, 1978. All correspondance should be directed to Dr. F. Korte, Institut fur Ökologsche Chemie GSF, Ingolstädter Landstrasse 1, D-8042 Neuherberg, F.R.G.

I. INTRODUCTION

The development of new plant protection agents during the past decade had among others the essential aim to produce new substances for the replacement of banned compounds or compounds suffering severely curtailed manufacture. These include, e.g., DDT and cyclodiene insecticides. On the other hand, there are preparations which have been known as insecticides for a long time and whose fields of application, especially after the ban on DDT, were expanded strongly. One preparation in this group is toxaphene.

Toxaphene was developed in 1945 by Hercules Inc., USA, and has been one of the most widely used insecticides in the United States since that time. It has played an increasing role in pest control in agriculture and forestry during recent years because of the limitations

put on other chlorinated hydrocarbons, such as DDT, aldrin, chlordane, dieldrin, etc. Its economic importance can be appreciated by the fact that since its introduction in 1946 cumulative world use until 1974 has been 450,000 tons. The range of applications of this pesticide covers practically all areas of agriculture. Concentrations ranging from 0.5 to 10 kg per ha are recommended and tolerated, depending on the type of plant. It can be applied either upon seeding or repeatedly for specific intervals. Its effect is immediate and preventative against many types of pests (Hercules, 1970), Toxaphene is, therefore, a broad spectrum insecticide with a wide application range and with a certain, although not a well defined, effective life span.

Toxaphene appears to be widely disseminated in the environment. This paper presents, after a description of its chemistry, use and toxicity, a survey of its occurrence as well as conversion and degradation in the environment.

II. CHEMISTRY

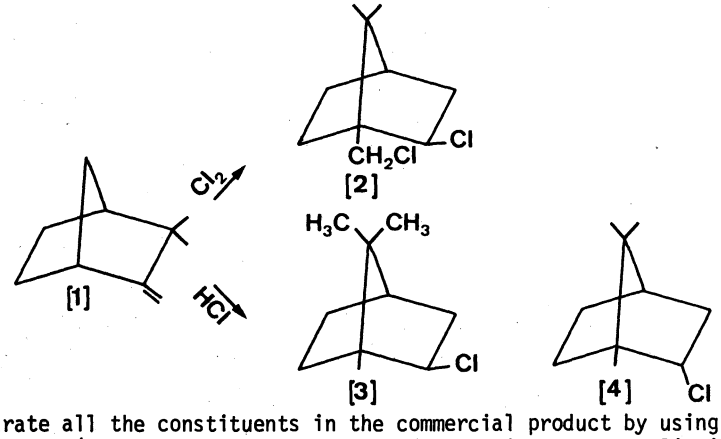
A) Properties of Commercial Preparation

a) Physical Properties

A yellow waxy solid of mild terpene smell; mp in range 65-90°C; density 1.65 cm^3; solubility in water 3 ppm at room temperature; readily soluble in organic solvents, including petroleum oils; vp about 10^{-6} mm Hg at 25°C.

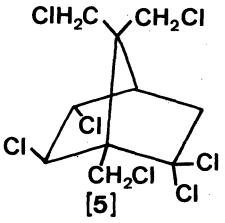
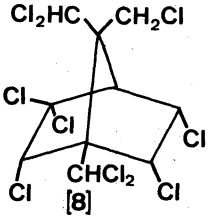
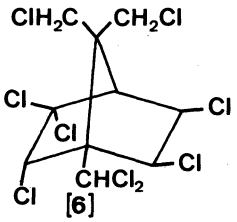
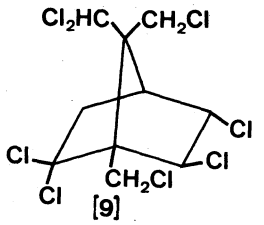
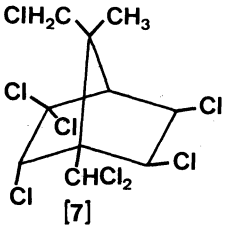
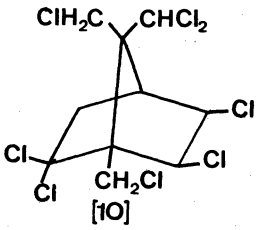
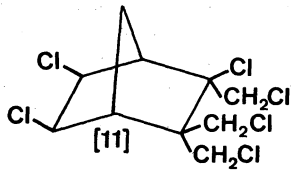
b) Composition of Toxaphene

Toxaphene represents chlorinated camphenes in technical purity grades. It is produced by passing chlorine gas through a solution of camphene in carbon tetrachloride upon UV-irradiation. The product obtained is marketed without further purification. It contains 67-69% chlorine, corresponding to the empirical formula $C_{10}H_{10}Cl_8$. The term for the purity grade "technical" refers to the quality of the final product, meaning that no attempt is made to fractionate or characterize the mixture with respect to a definite chemical composition after chlorination of camphene. Also an important point is that the camphene (1) used for the production is of technical quality only. Due to the lack of selectivity on chlorination, the number of isomers increases with a non-uniform degree of substitution. An example is the addition of chlorine to the double bond of camphene, which follows an unspecific pathway. This reaction was the topic of many investigations (Tishchenko and Uvarov, 1953; Jennings and Herschbach, 1965; Ghiurdoglu et al., 1957). Despite contradictory evidence, it has long been accepted that the addition of chlorine to the double bond leads to a conformation resulting in 2-exo, 10-dichlorobornane (2). From this reaction, it is assumed that toxaphene consists of higher substituted chlorobornanes. This assumption is further substantiated by the fact that an equivalent amount of HCl is evolved during the preparation. In this case 2-exo as well as 2-endo-chlorobornane (3,4) are formed in a Wagner-Meerwein rearrangment.



Attempts to separate all the constituents in the commercial product by using the known separation procedures (column and thin-layer procedures, high pressure liquid chromatography and preparative gas chromatography) have led to unsatisfactory results so far.

Although the chromatographic behaviour of the toxaphene components is extremely similar, seven components have been isolated up to now, six of which are hepta- to decachlor derivatives of bornane.

Compound	Percent in Toxaphene	Compound	Percent in Toxaphene
 [5]	3.0	 [8]	1.5
 [6]	3.0	 [9]	8.0
 [7]	0.5	 [10]	
		 [11]	0.8

Four groups took part in the isolation and identification of the toxaphene components. The compounds 6, 7 and 8 (compound I, II and III) were identified by a German group in 1974 (Anagnostopoulos et al., 1974), while compounds 5 (Toxicant B) and 9, 10 (Toxicant A) were isolated by another group (Casida et al., 1974; Khalifa et al., 1975). Toxicant A is identified by ^{1}H-NMR studies as a mixture of 2,2,5-endo,6-exo,8,8,9,10-octachlorobornane and 2,2,5-endo,6-exo,8,9,9,10-octachlorobornane. These components have many structural features in common with the previously identified compounds (5-8) (Turner et al., 1975). A third research group isolated the compounds 9 and 10 also during this time (Matsumura et al., 1975). Finally, a fourth research group identified a compound (11), which does not have the bornane skeleton, and they also identified again compound (5) (Landrum et al., 1975). The non-bornanoid structure of compound (11) was confirmed by X-ray structural analysis (Landrum et al., 1976).

From the combined application of gas chromatography and mass spectroscopy, it was determined that the toxaphene is composed of at least 177 polychlorinated compounds of the formula $C_{10}H_{18-n}Cl_n$; 26 of these compounds occur in concentrations higher than 1% (Holmstead et al., 1974). Attempts to dechlorinate the product resulted in a hydrocarbon $C_{10}H_{18}$ with a 20% yield (bornane) and several mono-, di-, tri- and tetra-chlorinated C_{10} compounds. Attempts at isolating the components of the commercial product have in general failed to yield reproducible results. There are several reasons for this: the investigated products originated from different batches and producers and, due to the complexity of the reactions taking place during the commercial productions, there is no guarantee that the product should have a quantitatively identical composition. It should also be mentioned that the starting material used for the separations was not always the usual commercial available product. The material obtained underwent one or more recrystallization steps before the actual separation procedure was undertaken. The recrystallized complex mixture is by no means constant with respect to composition.

The results of previous investigations on commercial toxaphene and from primary reactions of camphene chlorination (1) have shown that the product obtained consists of a mixture of polychlorinated bornanes. The question on whether the product contains further non-bornanoid polychlorinated compounds was confirmed through the isolation and characterization of compound (11). This substance probably results from camphene (1); in this case the primary conformation of mono- and dichlorobornanes (2, 3, 4) does not take place. Dehydro-derivatives with the empirical formula $C_{10}H_{16-n}Cl_n$, with n = 6-9, have also been reported (Holmstead et al., 1974). These compounds were detected by the use of the gas chromatography/mass spectroscopy combination, although it is uncertain whether these compounds are also present in the mixture. Their formation is more likely due to the employed analytical method: the required temperature for gas chromatography is above the decomposition temperature of the recrystallized toxaphens (approx. 160°C). By comparing the stabilities of various synthetically prepared low chlorinated bornane derivatives, it is to be expected that the dehydrochlorination of toxaphene components would result in the formation of polychlorinated bornylene or camphene. (The formation of 8-chloro-camphene from the dehydrochlorination of 2-exo, 10-dichlorobornane has actually been demonstrated; Michna, 1977).

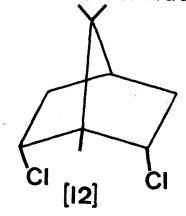
However, it should not be assumed that toxaphene components are limited to compounds with the structures of bornane or dihydrocamphene or tricyclene, since all these structures are formed from pure camphene (1).

The term "technical" does not refer to the final products, since the camphene (1) used is in turn obtained from terpene oil, and practically all terpene hydrocarbons are found in terpene oil. The β-pinene fraction is obtained from terpene oil by distillation. β-pinene is catalytically converted to the α-isomer. The technical procedure for the purification of pinene is a difficult operation, due to the similar physical properties of the terpene hydrocarbons.

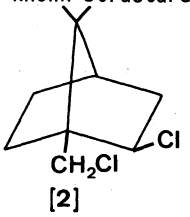
We do not know for certain whether the α-pinene is further purified prior to its final conversion into camphene (1). In any case, the catalytically induced rearrangement is by no means uniform. The monocyclic olefins and dienes and bicyclic compounds of the menthene and carene types are formed. Camphene (1) is obtained in a technical quality (75%). The impurities can be separated by distillation. Even if the impurites in the basic material camphene (1) would not be considered, it is likely that further C_{10} chlorinated hydrocarbons are present in toxaphene. Since the components isolated up to now constitute only a small part of the toxaphene mixture, it can be expected that in the future other substances will be isolated in similar amounts as the compounds known today. Technical mixtures originating from various producers were analysed by capillary gas chromatography. This provides a better characterization of technical toxaphene and gives important information concerning the gas chromatographic behaviour of the mixture (Saleh and Casida, 1977). Probably, combined capillary column GC with MS will be the most feasible tool to characterize chemically a larger portion of the toxaphene constituents.

B) Preparation of Individual Constituents

Low chlorinated bornane derivatives with known structures provide necessary information



[12]



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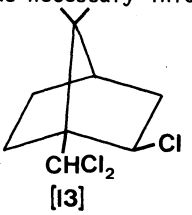

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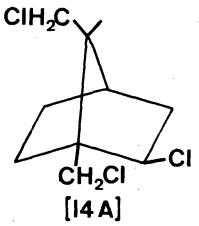
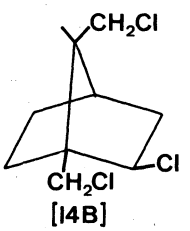


[14A]

or



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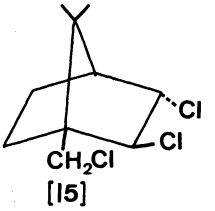

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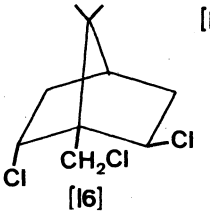

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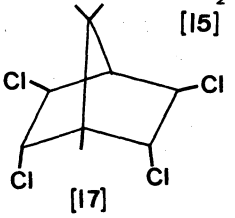
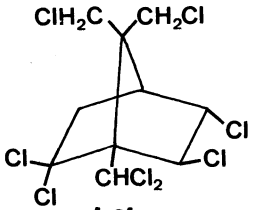


[17]

for the structural analysis of toxaphene and can also be employed as model substances to elucidate at least in part the potential environmental impact of toxaphene.

Besides the already-mentioned 2-endo,6-endo-dichlorobornane (12), 2-exo,10-dichlorobornane (2) and 2-exo,10,10-trichlorobornane (13), also 2-exo,8,10-trichlorobornane (14A) or 2-exo,9,10-trichlorobornane (14B), 2-exo,3-endo,10-trichlorobornane (15), 2-exo,6-endo,10-trichlorobornane (16) and 2-endo,3-exo,5-exo,6-endo-tetrachlorobornane (17) were prepared (Parlar et al., 1976).

Toxicant B (Compound 5), a major toxaphene component (~3%) is conveniently prepared in gram quantities of exo-2,10-dichlorobornane (2), chromatography of the reaction mixture on a silicic acid column with hexane, and crystallization (Turner and Casida, 1977). Chlorination of 5 yields compounds Toxicant A (9 and 10) and 18 and 19, which are likely to be toxaphene components.



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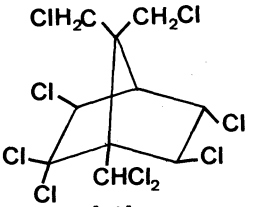
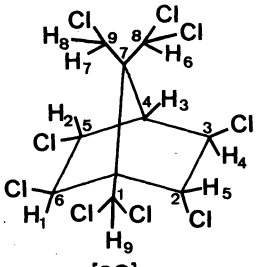


[19]

Nelson and Matsumura have also examined the products of chlorination reactions of purified exo-2,10-dichlorobornane (2) and determined the toxicities of these chlorinated products (four fractions). With the help of chromatographic methods a major peak with a retention time equal to a toxic component of Toxaphene could be isolated (Compound 5) (1975a and b).

Chandurkar et al. (1978) have recently reported that there is a persistent contaminant in the preparations of Toxicant A (9 and 10). They have isolated this compound and identified 2-endo,3-exo,5-endo,6-exo,8,8,9,10,10-nonachlorobornane (20) (Toxicant Ac).



[20]

C) Spectroscopic Elucidation

Low-chlorinated bornane derivatives were analysed by ^{1}H- and ^{13}C-NMR, MS and IR spectroscopy and the data obtained were compared with those of (6) (Parlar et al., 1977).

Mass Spectroscopy Studies on Low-Chlorinated Bornane Derivatives

The relative intensities of selected fragments of low chlorinated bornane derivatives as well as of compound (6) are compiled in the following table (I):

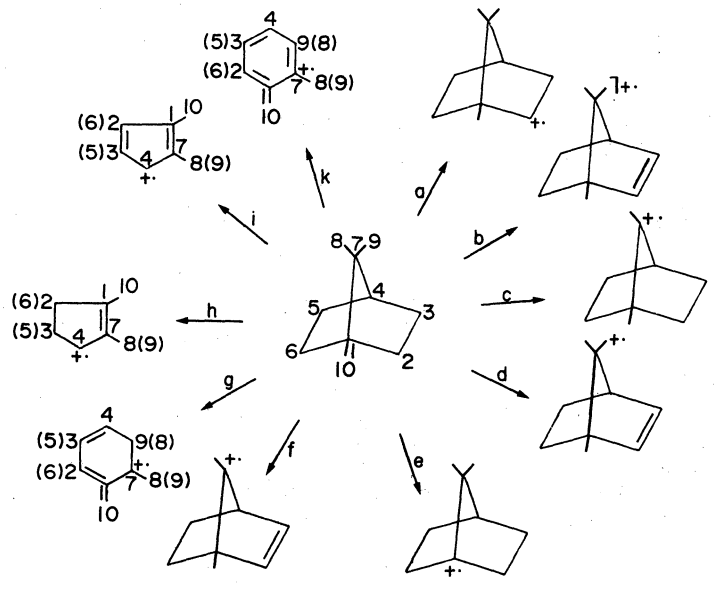
Table I: Mass Spectroscopic Data of Low-Chlorinated Bornane Derivatives

Compound	M^+	Rel. intensity	No. of Cl atoms	$(M-CH_3)$	Rel. intensity	No. of Cl atoms
13	240	1.6	3	225	25.2	3
14A or 14B	206	4.8	2	191	33.3	2
15	240	8.0	3	225	2.0	3
16	240	0.2	3	225	11.1	3
12	240	20.5	3	225	7.8	3
17	206	10.2	2	191	5.2	2
6	274	8.0	4			
				395 (CH_2Cl)	30.0	8

Compound	(M-Cl)	Rel. intensity	No. of Cl atoms	(M-HCl)	Rel. intensity	No. of Cl atoms
13	205	74.8	2	204	100.0	2
14A or 14B	171	92.7	1	170	100.0	1
15	205	92.4	2	204	100.0	2
16	205	82.3	2	204	100.0	2
12	205	47.1	2	204	100.0	2
17	171	66.7	1	170	100.0	1
6	239	19.6	3	238	100.0	3
	409	250.0	8	408	100.0	8

Compound	(M-Cl-HCl)	Rel. intensity	No. of Cl atoms
13	169	135.0	1
14A or 14B	135	3400.0	0
15	169	130.0	1
16	169	231.0	1
12	169	133.0	1
17	135	165.0	0
6	203	926.0	2
	373	250.0	7

The intensity of $(M-HCl)^+$ was used as reference fragment ion with an intensity of 100. The mass number 35 was used for the chlorine atoms contained in the molecules and fragment ions. A suggested pathway for the fragmentation of the chlorinated bornane derivatives is given in the following figure:



The fragmentation is characterized by elimination of small groups like Cl (path a), HCl (path b), CH_3, CH_2Cl and $CHCl_2$ (path c or e). The compounds 14A or 14B and 16 contain a CH_2Cl group as can be seen from the mass spectra. The fragmentation $(M-CH_2Cl)^+$ is observed with two chlorine atoms at m/e 191. This fragmentation is not only missing with compounds 12 and 17 which do not possess a CH_2Cl group, but notably also with compounds 2 and 15. Compounds 13 and 6 possess a $CHCl_2$ group at the C-1 position. The fragment ion $(CHCl_2)^+$ is recorded at m/e 83. The same elimination was found in the spectra of toxicants A (9 and 10) and B (5). Important clues to structures in this class of compounds are obtained from characteristic fragmentation, e.g., the ions of m/e 161 with two chlorine atoms of compound 13 (path i); m/e 127 with one chlorine atom of compound 2 (path i); m/e 129 with one chlorine atom (path h) and m/e 139 with one chlorine atom (path k) of compound 14A or 14B; m/e 161 with two chlorine atoms (path i) of compound 15; m/e 127 with one chlorine atom (path i) of compound 16; m/e 129 with one chlorine atom (path h) and m/e 127 with one chlorine atom (path i) of compounds 12 and 17. The ions m/e 277 with five chlorine atoms (path g), m/e 243 with four chlorine atoms (path g), m/e 265 with five chlorine atoms (path h), m/e 263 with five chlorine atoms (path i), and m/e 207 with three chlorine atoms (path k) were formed by the fragmentation of compound 6.

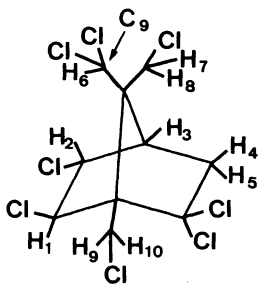
IR, ^1H- and ^{13}C-NMR Spectroscopic Studies of Low-Chlorinated Bornane Derivatives

It is possible to characterize the chloro substitution at the methyl groups of the bornane derivatives from IR-spectra alone. From the ^1H-NMR coupling constants of chlorinated bornane derivatives it is possible to determine the position of individual protons on the bornane skeleton. From the given spectroscopic data of the low chlorinated bornane derivatives and of the toxaphene fraction the composition of technical toxaphene can be better resolved. The data can also be of use in the interpretation of compounds isolated from toxaphene and of possible chemical, photochemical, and biological conversion products resulting from the toxaphene mixture (Parlar et al. 1977).

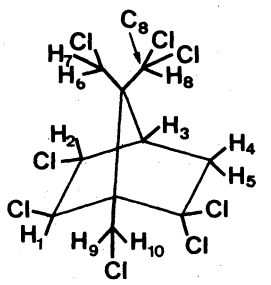
Spectroscopical Studies of High-Chlorinated Bornane Derivatives

Structure of the compounds 9 and 10 (Toxicant A) were determined by Turner et al. (1975). Toxicant A (9 and 10) is a crystallic material with the composition $C_{10}H_{10}C_{18}$ and gives a single peak on capillary GLC, but can be seen by its 100 MHz ^1H-NMR spectrum to consist of two major components. In analyzing the ^1H-NMR spectrum, the assumption was made that both components of Toxicant A are octachlorobornanes. The following table (II) gives a chemical shift data for these compounds (Matsumura et al., 1975).

Table II: Chemical Shift data for Components of Toxicant A



α



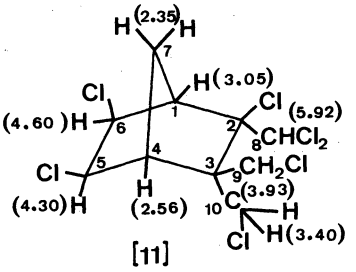
β

	α-Component		β-Component	
	CCl_4 a/	C_6D_6 b/	CCl_4 a/	C_6D_6 b/
H-1	5.44 d	5.43 d	5.56 d	5.43 d
H-2	4.98 t	4.85 dt	4.64 t	4.75 dt
H-3	~3.0 m	2.47 t	~3.0 m	2.30 t
H-4	~3.0 m	2.22 ad, dd	3.3 m	2.66 ad, dd
H-5	~3.43 ad	2.87 ad	~3.40 d	2.91 ad
H-6	6.96 d	6.44 d	4.87 ad, d	4.61 ad, d
H-7	4.79 ad, d	4.36 ad, d	4.35 ad	3.81 ad
H-8	4.38 ad	3.12 ad	7.17 d	6.65 d
H-9	4.49 ad	4.13 ad	4.22 ad	4.31 ad
H-10	3.65 ad	3.84 ad	3.95 ad	3.48 ad

a/ 270.071 MHz; b/ 90 MHz; d = doublet, t = triplet, m = multiplet, ad = asymmetric doublet (half of AB quartet)

The first toxaphene component known to retain the ring structure of camphene 2,5,6-exo,8,8, 9,10-heptachlorodihydrocamphene (11) was determined by single crystal X-ray diffraction method and ^{1}H-NMR spectroscopy (Landrum et al., 1976).

The crystals of $C_{10}H_{11}Cl_7$ have the space group P1 with a=8.75, b=11.16, c=7.94 and α=99.83, β=114.65, γ=85.16° (reduced cell) and Z=2. Intensity data (2863 reflections in one hemisphere) were collected at about 85K, with an automatic four circle diffractometer, using Mo Kα radiation and the θ-2θ scan method, to 2θ max of 55°. The structure was solved by direct methods using 2576 reflections with intensities >3σ and refined to a reliability index of 0.022.



[11]

Methylene protons on C-9 are unsplit due to free rotation, from examination of molecular models, about the C-3, C-9 bond. Methylene protons at C-7 are magnetically equivalent and appear as a singlet, in contrast with the less symmetrical NMR model. The observed coupling between vicinal endo protons at C-5 and C-6, 6 Hz, is close to that reported for the endo protons of the norbornane system -CHCl-CH(CCl_3)-, 7 Hz. Proton assignments at C-5 and C-6 may well be reversed, as might those at C-1 and C-4.

III. PESTICIDAL FORMULATION AND USES

Toxaphene is marketed in the following formulations: 40% wettable powder, 4%, 6%, and 8% emulsifiable concentrates, 5-20% dust, 10% and 20% granules, and 1% baits. It is also mixed with other pesticides. 70-90% of the toxaphene used in USA is applied to cotton. It is also used as a foliage or soil insecticide on 168 agricultural commodities, mainly on the following crops: alfalfa, bananas, barley, beans, broccoli, brussel sprouts, cabbage, carrots, cauliflower, celery, citrus, collards, corn, cowpeas, cranberries, egg-plant, hickory nuts, horseradish, kale, kohlrabi, grass, lettuce, oats, okra, onions, ornamentals, parsnips, peaches, peanuts, pears, peas, pecans, peppers, pimentoes, pine-apples, quince, rice, rutabagas, rye, sorghum, soybeans, spinach, strawberries, turf, tomatoes, wheat.

Furthermore, it is used to control exoparasites on cattle, sheep and goats. The most important pests controlled are: leafhoppers, loopers, armyworms, corn earworms, cutworms, grasshoppers, European cornborer, lygus bugs, aphids, spittlebugs, thrips, leafminers, chinch bugs, bollweevils, bollworms, chiggers, crickets, ticks and many others (Thomson, 1976). The application rates are 1.19-9.58 kg actual/m^3 water.

Because of its relatively low toxicity to bees, toxaphene preparations are of particular interest for treating flowering plantations. The insecticidal effect persists for a long time. Its action on cockroaches is weaker than that of DDT, whereas for some other types of insects higher activities were found (Keller and Liang, 1962); therefore, it has not been used for cockroach control. Toxaphene was once recommended for the control of rodents (mice; Maier-Bode, 1965). Toxaphene has also been used in fish eradication programs (Muirhead-Thomson, 1971).

IV. BIOCHEMICAL ASPECTS AND TOXICITY

a) Warm-Blooded Animals Including Man

Studies on the tissue distribution and storage of toxaphene in the body have demonstrated that a saturation level is reached in the body, that the fat is the preferential organ of storage and that the degree of storage is relatively low - 1/4 to 1/8 of feeding level for rats. After termination of exposure to toxaphene, elimination is prompt, and toxaphene residues in fat disappear rapidly. Excretion of toxaphene in milk of cows closely parallels the level of storage in fat tissue. As is the case with other chlorinated hydrocarbons, toxaphene induces activity of liver microsomal enzymes. The microsomal stimulation is reversible. Minimum induction was observed to occur at 5 ppm feeding level of toxaphene, compared to a similar induction at 1 ppm with DDT (FAO/WHO, 1969; USDA, 1977).

Toxaphene is reported to have, for warm-blooded animals, an acute toxicity which is about three to four times higher than that of DDT (Gruch and Steiner, 1960). Table III shows the LD_{50} in mg/kg for different warm-blooded animals and different kinds of application (Gruch and Steiner, 1960; Maier-Bode, 1965; FAO/WHO, 1969). The variations between the data reported are due to differences in age of animals, vehicle, and other factors.

Table III. Acute Toxicity of Toxaphene in Warm-Blooded Animals (mg/kg bodyweight)

Animal	Acute oral LD_{50}	Acute i.v. LD_{50}	Acute dermal LD_{50}
Rat	40-150	13	1075o 780o
Mouse	112	-	-
Rabbit	25	-	as solution: <250 as dust: <1000-2000
Guinea-pig	69-375	-	-
Dog	15-40	5 - 10	-
Goat	200	-	-
Sheep	100-200	-	-
Calf (3 months)	50	-	-
Pigeon	200-250	-	-
Quail	80-100	-	-
Man (estimated)	60	-	-

The signs of toxicity following acute exposure to toxaphene are the results of diffuse stimulation of the cerebrospinal axis and include various symptoms (FAO/WHO, 1969).

Fatal intoxications of humans have been caused by "cotton dust" containing 5% DDT, 10% toxaphene and 40% sulphur. The "subacute fatal human dose" for this mixture is reported to be 0.75 g DDT + 1.5 g toxaphene (Heyndrickx, 1960).

Toxaphene in solution form is readily absorbed through the skin, whereas absorption from dust and granules is reduced. Data on its cutaneous toxicity are included in table III.

Short-term and long-term chronic toxicity studies were carried out with different animal species including rats, dogs, cows, and monkeys. No toxic effect was observed at dietary levels of 25 ppm for the rat, 40 ppm for the dog, and 15 ppm for the monkey (FAO/WHO, 1965). Using higher doses, cytopathologic changes of liver, kidneys, and brain were detected, primarily liver enlargement which is observed also with many other chlorinated hydrocarbons. Upon daily feeding of two female monkeys with 10 ppm toxaphene in the diet for 2 years, no differences in growth and organ weights were observed as compared to controls (Maier-Bode, 1965).

Application of an aerosol spray containing toxaphene to the skin of 50 human subjects daily for 30 days at a dose of 300 mg/day produced no toxic manifestations. Fifty human volunteers who inhaled 0.0004 mg/liter of toxaphene aerosol for 10 minutes a day for 15 days had no subjective or objective effects. A mist containing 0.25 mg toxaphene per liter of air was inhaled by 25 humans for 30 minutes each day for 13 days and they showed no evidence of local or systemic toxic manifestation (Shelanski, 1947; USDA, 1977).

In a three-generation, six-litter reproduction study with rats, reproduction was not affected at the 100 ppm dietary level, but liver damage occurred (Kennedy et al., 1973). In a five-generation reproduction study with mice at 25 ppm dietary level, no effects were noted on any of the reproduction parameters measured (Keplinger et al., 1970). In other reproduction studies, also adverse effects on the offspring were always related to maternal toxicity (USDA, 1977). In pheasants, egg-laying and hatchability were significantly depressed at 300 ppm toxaphene in the diet; already at 100 ppm, the mortality of the young pheasants was significantly greater than that of controls (Genelly and Rudd, 1956).

No teratogenic potential was observed when toxaphene was injected into eggs at doses up to 1.5 mg/egg (Smith et al., 1970).

Toxaphene showed no mutagenic effects in dominant lethal assays using Swiss mice at dosage ranging from 36-180 mg/kg administered orally or intraperitoneally (Epstein et al., 1972). Toxaphene is mutagenic in the Ames histidine-requiring TA-100 strain Salmonella typhimerium assay (Hooper et al., 1978). Unpublished data from a carcinogenicity study showed an increase in liver tumors by toxaphene in mice. However, epidemiological data do not

indicate that toxaphene is a carcinogen (USDA, 1977).

b) Fish

Fish toxicity of toxaphene has been reported in numerous studies (e.g. Thomson, 1976; Maier-Bode, 1965; Mehrle and Meyer, 1975 a and b). Adverse effects attributed to toxaphene are stunted growth and skeletal fragility ("broken back syndrome"; Mehrle and Meyer, 1975 a and b). Bioaccumulation by fish living in toxaphene-contaminated water was about 7,000 according to Terriere et al. (1966). In fish-eating birds, toxaphene does not bioaccumulate (Keith and Hunt, 1966).

c) Phytotoxicity

In general, toxaphene is not phytotoxic, except for certain varieties of cucurbits and plums. It may cause off-flavour in stored tobacco and deterioration of flavour for other crops (Thomson, 1976; Maier-Bode, 1965). Toxaphene at 1 ppm inhibits the growth of fresh-water blue-green algae, Anacystis nidulans, under laboratory culture conditions (Nelson and Matsumura, 1975 b).

V. DETECTION

For the detection of toxaphene in environmental samples, total organic chloride determination (Brett and Bowery, 1958; Muns et al., 1960; Carlin et al., 1974), colorimetric methods (Hornstein, 1957; Graupner and Dunn, 1960; Nikolov and Donev, 1963), and bioassays (Eichenberger, 1960) were used. Today, gas chromatographic methods using microcoulometric EC detectors are most prevalent. Clean-up is performed by partition in acetonitrile-water-petrolether or hexane-water and by column chromatography with florisil or Al_2O_3 (1% acetone in hexane) (29th Pesticide Analytical Manual I 1967; Adato, private communication).

The detection and quantitation of sub-microgram quantities of toxaphene by GC is difficult especially in the presence of other pesticides. Because of its composition, toxaphene chromatographs as a series of hills and valleys with three main peaks (Gomes, 1977). In order to improve the general methods, modified GC methods were developed. The use of a flash heater, filled with various reagents in the injection part of the gas chromatograph, produces definite changes in the chromatogram of the pesticides (Minyard and Jackson, 1965). Alkali treatment is used for rearrangement or partially dehalogenation of toxaphene (Crosby and Archer, 1966; Miller and Wells, 1969; Young and Burke, 1972). Treatment of toxaphene residues with 50% methanolic potassium hydroxide for 1 hr, followed by elution of the mixture through a florisil column, results in isolation of a single major peak which permits quantitation with a detection limit of 1 ng (Gomes, 1977).

A report on analytical methods for the determination of toxaphene components in environmental samples has also been given by Dolan et al. (1974).

VI. OCCURRENCE IN THE ENVIRONMENT

A) Plants

Numerous residue data on toxaphene-treated plants have shown that toxaphene may persist on plants. Half-life on leafy crops is reported to be betweeen 5 and 13 days, depending on weathering conditions, plant type, growth rate, and formulation (FAO/WHO, 1969). After application at recommended rates, residues of about 2 ppm may be expected after 30 days (Maier-Bode, 1965). The mechanism of residue disappearance was investigated by Carlin et al. (1974), by Nash et al. (1977), and others.

Carlin et al. (1974) did residue decline studies on alfalfa, range grass, and winter wheat treated with toxaphene emulsion sprays. Toxaphene residues were measured by electron capture gas chromatography (ECGC) after partial dehydrochlorination (de-HX) in potassium hydroxide-ethanol solution and were confirmed by total organic chloride (TOCl) determination after reduction by sodium-liquid ammonia. All residues were identified as toxaphene by ECGC. ^{36}Cl-Toxaphene was applied to living cotton plants, and the treated plants were maintained in a closed all-glass system for 7 days. Samples from various sites throughout the system were analyzed by de-HX/ECGC and by liquid scintillation counting (LSC) procedures. ^{36}Cl-Toxaphene components were distributed throughout the apparatus, but the majority of the residue was detected on the cotton plants. The residue on the plants was identified by ECGC as toxaphene. No evidence of metabolism was detected. The mechanism of loss was suggested to be by volatilization.

In order to get further information on the volatilization of toxaphene from treated plants into the atmosphere, Nash et al. (1977) applied toxaphene to cotton plants at

weekly intervals for six weeks in an enclosed chamber (agro-ecosystem), and the volatilization was monitored for 90 days. The volatilization seemed to follow log concentration with log time the first week and then log concentration with linear time thereafter. Calculated first-order equation half-life for volatilization of toxaphene was 15.1 days.

Bioaccumulation of toxaphene by plants (lake vegetation) was found to be about 3,000 times (Terriere et al., 1966).

B) Soil

Residues of toxaphene in soil may persist for years; also in this case, volatilization is suggested as a major loss mechanism (Guyer et al., 1971). In cropland under regular use, the recovery rate, 1-3 years after the last application, is in the order of 10-30% (Stevens et al., 1970; USDA, 1977). The evaporation from the surface of soil is rapid providing the surface is not dry. The process of volatilization is nearly stopped if the soil is cultivated or the toxaphene is mixed with the soil (USDA, 1977).

C) Air

The occurrence of volatilized residues in the atmosphere was demonstrated at various locations in the United States (Stanley, 1968; Stanley et al., 1971). The correlation to agricultural sprayings was studied by Arthur et al. (1976). Over the most intensive cotton growing area of Mississippi, the residue levels of toxaphene were highest in August for three consecutive years (1972-1974), indicating the spray activities in the area. The levels of toxaphene found were in the same order as those of methylparathion. However, toxaphene is not found exclusively in the air over application sites, but may be transported over long distances. Bidleman and Olney (1975) reported a long-range transport of toxaphene through the atmosphere, at least 1,200 km from the application sites out to sea: during 1973-1974, toxaphene was detected in air samples collected over the western North Atlantic. The mean concentration of 56 samples was 0.63 ng/m^3, as against 0.024 for p,p'-DDT; the ratio of these concentrations is close to the ratio of the outdoor evaporation rates of the two pesticides.

D) Water

Besides transport by air, movement from soil to water may be regarded as another source of toxaphene dispersion. The primary route of entry of toxaphene into water is through surface runoff. Sediment carries nearly all the toxaphene in the surface runoff. It is possible to measure toxaphene yields of runoff in sediment and to get the rough estimates of time that it takes for toxaphene concentrations to be reduced to biologically inactive levels once sediment contaminated with toxaphene is introduced into the water. For the most part, these time periods are relatively short varying from a few days to a few months depending on the size of the surface area of the body of water, the organic matter in the water, the sediment load, and the toxaphene concentration in the sediment (USDA, 1977).

Movement of toxaphene through the soil to ground water was studied by La Fleur et al. (1973). According to this study, toxaphene loss from top soil treated with 100 kg/ha seems to occur in two stages. The second (major) stage is about linear on a log residue vs. log time plot. Half-residence time in the top soil is about 100 days. Toxaphene was found in underlying ground water within two months after application to the top soil and persisted in ground water during one year of monitoring. However, it should be emphasized that this extremely high level is very unlikely to occur under normal environmental conditions, except accidents or areas near manufacturing plants.

In surface waters of streams in western USA, toxaphene was not found within two years (1966 - 68) among the samples collected in 20 stations (Manigold and Schulze, 1969).

Bioaccumulation ratio in lake sediments was measured to be about 700 (Terriere et al., 1966). However, when the Mississippi river sediment was analyzed (Barthel et al., 1969), toxaphene was not detected, notably in the delta area where the greatest concentration of other pesticides was reported by another author (Edwards, 1970). There were two samples where indeed point source contaminations resulting from manufacturing and formulating activities on toxaphene have been found to occur. It seems that such point source contaminations do not spread noticeably, as attested to by the absence of contamination in the downstream localities and by other studies on toxaphene-contaminated factory outlets (Durant and Reimold, 1972).

Disappearance from water is mostly due to volatilization, like for plant and soil residues. The rate at which it moves to the surface layer of water is controlled by several factors including rates of diffusion and rate of desorption. However, it was observed that a very

small amount stayed in a lake for a fairly long period of time (USDA, 1977).

In spite of volatilization and other residue disappearance mechanisms, toxaphene may find its way into the drinking water: 27 of 680 samples throughout the USA were positive, 2 had residues above 0.05 ppb (EPA, 1975). In more than 500 samples along the Mississippi and Missouri rivers, however, toxaphene was not detected (Schafer et al., 1969).

E) Wildlife

In wildlife, toxaphene occurs very infrequently. However, the frequency of finding toxaphene in fish and mollusks was about 16 out of 1,000, and residue levels ranged from 0.01 to 1.25 ppm in fish and 11 to 54 ppm in mollusks. There is evidence to indicate that toxaphene has not caused severe population reductions or affected the survivability of land-living animal species. The role which toxaphene plays in the different fish kill episodes, in comparison to other pesticides, is not fully clarified (USDA, 1977).

F) Humans

Contrary to DDT, hexachlorobenzene and some cyclodienes, toxaphene has not been detected in human tissues (Hayes, 1975; Kutz et al., 1976; USDA, 1977). This fact may be due partly to quick elimination, partly to the relatively rare occurrence of toxaphene residues in human food. Market-basket surveys in the USA between 1965 and 1969 revealed an incidence rate of less than 2% and an average concentration of less than 0.2 ppm for most food groups. However, oils and oily crops showed a higher incidence of toxaphene (cotton seed 29%). In processed (canned, dried or frozen) food, toxaphene residues were 6th most frequent in occurrence of all pesticides. but few were in excess of the 7 ppm limit. From 1965 to 1970, the average daily intake was calculated to be 0.0015 mg/day (FAO/WHO, 1974; Duggan et al., 1971; Duggan and Corneliussen, 1972). Further total diet studies of the National Pesticide Monitoring Program from 1966 to 1974 revealed a frequency of 9 times/1,000 samples with a range of residue levels from a trace to 0.20 ppm (USDA, 1977).

VII. DEGRADATION IN THE ENVIRONMENT

A) Soil

Toxaphene undergoes anaerobic degradation in the soil, and this degradation is extensive if the soil is high in humus or organic matter (Parr and Smith, 1976).

Anaerobic metabolism of toxaphene fractions in soil was studied by Murthy et al. (1977). ^{14}C-Toxaphene prepared by chlorination of 8-[^{14}C]-camphene was separated into nine fractions of roughly equal radioactivity by dry column chromatography on silica gel. These nine fractions were individually incubated for 42 days in flooded Metapeake silt loam under anaerobic conditions. CO_2 production and volatility losses were minimal (0.01 - 0.34% and 0.18 - 0.37%). Binding of ^{14}C was most pronounced with soil humin and showed no trends between toxaphene fractions. Thin layer chromatography revealed the presence of several metabolites from each fraction. Changes in composition of the fractions during incubation, primarily by dechlorination, were evaluated by gas chromatographic-mass spectral analysis. Metabolism studies by aquatic sediments and a camphor-degrading Pseudomonad (Clark, 1977) indicate that toxaphene is first dechlorinated and then oxidatively degraded. The time required for the complete disappearance of toxicant A (compounds 10 and 9), B (compound 5) and C (compound 6) were 10 to 30 days in a model aquatic system with sediment. Definite changes in gas chromatographic pattern were observed during the course of microbial degradation. The oxidative degradation products are either alcohol or carboxylic acid derivatives of chlorinated bornane.

B) Animals

In a study of toxaphene storage in animals, Bateman et al. (1953) found that sheep and steers fed 10 ppm daily in the diet showed no accumulation in the fat after 30 days exposure. However, with repeated dosage, storage in the fat of these animals and also dairy cows was reported by Conley (1952) and Diephuis and Dunn (1949). Conley suggested, without detailing the evidence, that toxaphene is slowly detoxified in the liver by excretion of ethereal sulfate and glucuronate. Clayborn (1963) found toxaphene in milk of dairy cows given 20-140 ppm in feed. Uncontaminated milk was observed by Zweig et al. (1963) within two weeks after animals were removed from the toxaphene diets.

Pollock and Kilgore (1976) orally intubated female rats with ^{14}C-toxaphene and several isolated toxaphene fractions. The animals were housed in glass metabolism chambers and the urine and feces were collected, extracted, and analyzed by a combination of TLC scanning and liquid scintillation counting. In addition, in vitro metabolism using liver homogenates

was studied. The results show that there are differences in the excretion between some of the toxaphene components.

Due to the limited information available on the fate of toxaphene in the mammalian system, Crowder and Dindal (1974) studied the fate of ^{36}Cl-toxaphene in rats. They reported routes and rates of excretion as well as the amount and loci of accumulation in various tissues of male rats. In the rat, 52.6% of an oral dose of ^{36}Cl-toxaphene was excreted within 9 days. Approximately 37% was found in the feces and 15% in the urine. Upon extraction, most of the radioactivity occurred in the water fractions of urine and feces as ionic chloride indicating that considerable toxaphene metabolism had occurred. Animals given a second dose on the 9th day excreted toxaphene in a similar manner except ^{36}Cl-excretion in feces was reduced. Less than 10% of the dose was found in selected tissues and organs 1 day following the treatment. Most was found in the stomach and very little in the brain tissue or fat storage cells.

Ohsawa et al. (1975) found that rats treated orally with ^{36}Cl-toxaphene and each of seven fractions of ^{36}Cl-toxaphene of equal total chlorine content excrete about 50-60% of the ^{36}Cl in urine and 30-40% in feces within 14 days. In each case about half of the dose is excreted as chloride ion determined as phenylmercuric ^{36}Cl-chloride. Similar studies with ^{14}C-toxaphene and one or both of two components of high mammalian toxicity, toxicant A and B, establish that the feces contain unmetabolized compound and that the metabolites probably include acidic materials, products formed by partial or complete dechlorination, and ^{14}C-carbon dioxide. The acidic materials have possible structures of mercapturic acids, terpene carboxylic acids and their glucuronides or sulphates. Most if not all of the components undergo extensive or complete metabolic dechlorination or dehydrochlorination or both. The expired products including $^{14}CO_2$ arise from methyl, chloromethyl, or dichloromethyl substituents in the original toxaphene components. The tissues retain relatively low levels of ^{14}C several days after administration of ^{14}C-toxaphene or ^{14}C-labelled toxicant B. The structural features important for high toxicity to house flies and mice are present in only a few toxaphene components while those conferring biodegradability appear to be shared by most if not all components.

In another rat metabolism study, it was found that dechlorination and oxidative degradation by mixed-function oxidase involving cytochrome P450 are active degradation mechanisms for toxaphene (Chandurkar and Matsumura, 1977).

Khalifa et al. (1976) examined the reactions of toxaphene and two of its most toxic compounds, toxicants A and B, with two iron (II) protoporphyrin systems, hematin reduced with $Na_2S_2O_4$ and microsomal cytochrome P450 reduced with NADPH. They found that toxaphene reacts with reduced hematin in neutral aqueous medium to cleave about half of the C-Cl bonds, yielding derivatives of shorter retention times on gas chromatography and of reduced sensitivity for detection by electron capture. The system also converts toxicants A and B to products formed by reductive dechlorination, dehydrochlorination, and a combination of these reactions. Extensive metabolism of toxaphene and toxicants A and B by rat liver microsomes requires both NADPH and anaerobic conditions suggesting that reduced cytochrome P450 acts as the reducing agent.

From these results it is clear that many toxaphene components, including octa- and heptachlorobornanes such as toxicants A and B, are converted by one or both of these iron (II) protoporphyrins to more polar derivatives, based on TLC. The studies with reduced hematin establish that toxaphene undergoes extensive dechlorination and that the products from toxicants A and B determined by GC-CI-MS are formed by two or more of these processes: reductive dechlorination, dehydrochlorination, and vicinal chloride elimination. Many of the reaction products can be obtained in microgram amounts in the anaerobic microsome-NADPH system and in milligram or potentially even in gram amounts in the reduced hematin system.

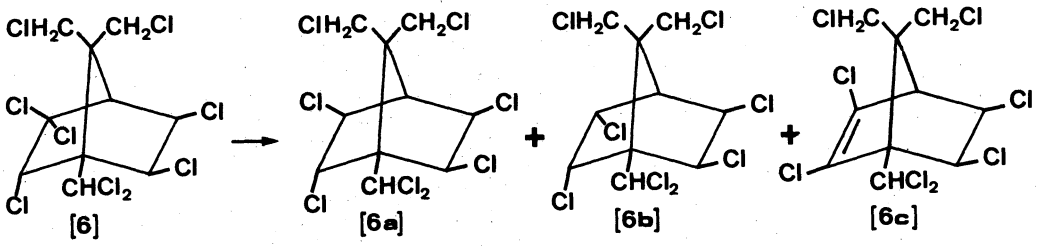
Thus, the model iron (II) protoporphyrin systems provide a means of generating degradation products of toxaphene and its components and thus understanding how toxaphene degradation proceeds under certain metabolic and environmental conditions.

Toxaphene metabolism in chickens and 6 species of mammals including monkeys involves extensive dechlorination and, in the case of rats, app. 50% of the dose is excreted as chloride ion (Saleh and Casida, 1978, a,b; Saleh et al., 1977).

C) Photochemical Degradation

The behaviour of chlorinated bornane derivatives in solution and adsorbed on silica gel were investigated by Parlar et al. (1976). The dechlorination products 6a and 6b were found together with the dehydrochlorinated compound 6c. Similarly, compound 5 under the

same conditions gives the corresponding pair of reductive dechlorination products (Saleh and Casida, 1978b). Although 2-endo, 6-endo-dichlorobornane (12) and 2-exo, 10-dichlorobornane (2) do not react under these conditions, they do decompose like the technical mixture to HCl and CO_2 when adsorbed on silica gel and irradiated at wavelengths above 230 nm.



Irradiation of 6 in n-hexane: A solution of 30 mg of 6 in 3 ml oxygen free n-hexane was irradiated at wavelengths above 230 nm. Approximately 30% of 6 was converted within 24 hours. The yield of the photoproducts 6a, 6b, and 6c were 6.0, 5.4, and 8.1%, respectively (by GC). The irradiation mixture contained also low-chlorinated products which were not identified. The irradiation of 6 in methanol/water yields the same photoproducts: 3.0% for 6a, 2.2% for 6b, and 2.5% for 6c, respectively.

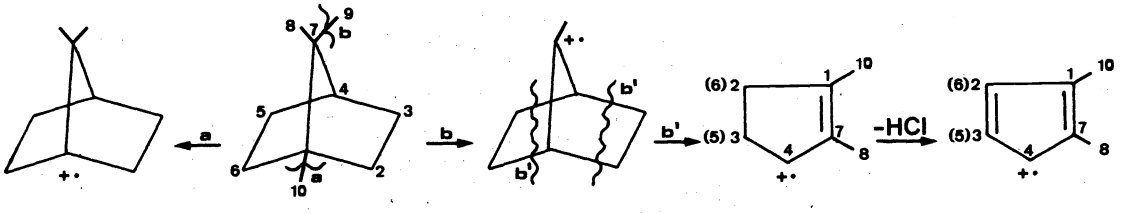
The results of the irradiation experiments (λ >230 nm) adsorbed on silica gel are summarized in table IV:

Table IV: Photomineralization of Technical Toxaphene and its Components (λ >230 nm)

Compound	Amount (mg)	Detected mineralization products in mg CO_2	HCl
2-endo,6-endo dichlorobornane (12)	270	528	76
2-exo,10-dichlorobornane (2)	494	571	80
Technical toxaphene	552	154	271

Attempts to photomineralize technical toxaphene at wavelengths above 290 nm were unsuccessful.

Structure of the photoproducts 6a, 6b and 6c: The structure of photoproducts were determined by mass spectroscopy.



Compound	Fragment ion	Compound	Fragment ion	Compound	Fragment ion
6	361	6	299, 265	6	263, 229
6a, 6b	327	6a, 6b	- 265	6a, 6b	- 229
6c	325	6c	- 265	6c	263, 229

Compounds 6a and 6b are isomers formed by the monodechlorination of 6. Although the data available do not represent a structural characterization of compounds 6a and 6b, it is possible to predict the dechlorination positions from the fragmentation patterns. The fragmentation pathway a leading to the fragment ion 361 with 7 chlorine atoms and 327 with 6 chlorine atoms (6a and 6b), is an indication that the photodechlorination of 6 does not take place on C_{10}. The mass spectrum of 6 shows an ion of high intensity at m/e 299 (fragmentation pathways a and b) which decomposes with the cleavage of HCl to an ion with the mass 263 (Cl_5). The absence of both these fragments in the spectra of 6a and 6b indicates that these compounds do not possess the $\overset{Cl}{\underset{Cl}{C}}$ group as does compound 6. It can therefore be shown that the dechlorination takes place on C_2 and C_5.

Compound 6c has a chlorinated double bond between C_5 and C_6 and has the structural requirements necessary to form an ion with the mass 263 (Cl_5). Furthermore, the fragment ions 265 (Cl_5) and 229 (Cl_4) are characteristic for compounds 6, 6a, 6b and 6c.

VIII. SUMMARY AND CONCLUSIONS

1. Toxaphene is a complex mixture (> 177 C_{10} polychloro compounds) from which five components have been chromatographically isolated in the indicated yields and identified by ^{1}H-NMR and MS (5,6,7,8 and 11) or by these procedures plus X-ray crystallography (5 and 11). Two additional octachlorobornanes (Toxicant A), isolated as a ca. 50/50% mixture (9 and 10), are identified by ^{1}H-NMR and MS. A nonachlorobornane (20), isolated in undefined yield from toxaphene, is identified by ^{1}H-NMR and MS. Chlorination of 5 yields a product mixture suitable for isolating 10-Cl and 3-exo-Cl derivatives (18 and 19), identified by ^{1}H-NMR and MS, which are chromatographically identical with two toxaphene compounds. These ten compounds or fractions account for ca. 20 - 25% of the toxaphene components as approximated by GLC-EC of toxaphene or partially fractionated toxaphene. The most toxic of the identified components to houseflies, goldfish and mice is 2,2,5-endo,6-exo-8,9,9,10-octachlorobornane (5). This octachlorobornane, which is estimated to represent about 3% of technical toxaphene, contributes a significant portion of the overall toxicity of toxaphene to these organisms.
2. Toxaphene is slowly to rapidly degraded in various environmental systems. It has been found in soil, in air, and in waters. Bioaccumulation is lower than for various other organochlorines. Occurrence in human tissues has not been reported. Due to relatively high vapour pressure (about 10^{-6} mm Hg), it is apparently volatilized rapidly from plants, soil, or water. This volatility results in lower residues in these media than for other chlorinated pesticides.
3. Analytical methods for determining the consistency of the technical product are sufficiently developed.
4. Available analytical methods for detection in environmental samples are, because of the high number of components, metabolites and degradation products, not sufficient.
5. Although main commercial products manufactured in the western world may have reproducible and constant composition, some products produced in other countries may differ in their composition.

RECOMMENDATIONS

1. Other components of technical toxaphene should be identified and their insecticidal and mammalian toxicities should be determined.
2. In practise the number of constituents should be as low as possible to avoid unnecessary contamination.
3. Analytical methods should be improved for detection in environmental samples.
4. Metabolism and ecotoxicological investigations should be enhanced.

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