DOI: 10.2478/cttr-2013-0190
Beiträge zur Tabakforschung · Band 4 · Heft 6 · November 1968

The Nature and Significance of Pesticide Residues on Tobacco and in Tobacco Smoke*

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INTRODUCTION

Pesticide residues have been recognized as a potential problem by the tobacco industry since *Remington's* observation concerning residues of inorganic pesticides on commercial cigarettes in 1927 (68). The advent of the organic pesticides around 1950 not only promised the grower solutions to critical pest problems during culture of tobacco but also introduced new problems relating to tobacco quality. The important problems of quality relating to sucker control (22) and off-flavor (28, 80) as a result of pesticide use are beyond the scope of the present paper and will not be discussed at this time. Instead, attention will be directed to the magnitude of pesticide residues which result when growers apply organic chemicals to control pests plaguing culture of tobacco, the fate of these residues throughout the various commercial procedures, and their significance in the final product offered the consumer. An attempt will be made to draw an analogy between the residue problems on food and on tobacco and to present possible guide-lines to follow should governmental regulations be extended to tobacco. The possible role of pesticides as carcinogens in tobacco smoke has been recently reviewed (86), as has the specific relationship of pesticide residues to the health aspects of tobacco (73).

This is an appropriate occasion for consideration of pesticide residue problems. Increasing scrutiny of pesticide residues by regulatory agencies of several governments (5,66,71) makes it seem likely that a greater awareness of existing and potential problems on tobacco is to be expected. It is justifiable and proper for federal agencies to assume responsibility for any possible health hazard to large segments of the population. The tobacco industry must maintain continuous quality surveillance to permit early detection of materials which might offer adverse effects. Prompt, decisive action coordinated with regulatory agencies can usually prevent unwise legislative restrictions on tobacco which might present a serious impediment to marketing and manufacturing procedures.

Culture of Tobacco

A brief synopsis of the culture and manufacture of tobacco is presented at this point to permit the uninitiated to comprehend the residue problem on tobacco.

To control the insect complex, one or more insecticidal treatments are applied during the harvesting (priming) period, and the biological effectiveness of the treatments should be 7 to 14 days. One application of a growth regulator for control of adventitious suckers is commonly applied at the time the terminal bud is removed (topping). On the infrequent occasions when fungus diseases are a problem, applications of fungicides are made every week until the disease disappears. Residues from pesticide applications to tobacco are rather high due to the large surface-to-weight ratio of this, and any other, leafy product. Flue-cured and cigar-wrapper tobacco is harvested by pulling 2 to 6 of the riper leaves at the desired number of intervals (once per week or 2 to 3 times per season). Burley and dark tobacco is normally harvested at the end of the season, all leaves being removed from the stalk at the same time. Tobacco is either flue-cured (leaves subjected to temperatures of 140° to 180° F over a period of 4 to 5 days) or air-cured for one to several weeks in the case of burley and cigar tobaccos. During August to October (in the U. S.), flue-cured tobacco is displayed by the farmer at warehouses and sold to tobacco companies by an auction system. Burley tobacco is sold under a similar system from

* Presented at the CORESTA Symposium on Products for Tobacco Treatment, Stockholm, September 1968.

November to February. The tobacco is then packed in 50 cubic feet barrels (hogsheads) and aged from six months to several years. The aging process is an active fermentation. As needed, the tobacco is removed from the hogsheads and made into the desired tobacco product.

Pesticides Most Commonly Used on Tobacco and Their Toxicity to Mammals

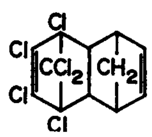
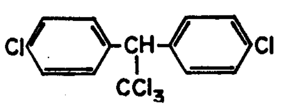
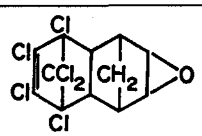
Although approximately 50 pesticides are, or have recently been, registered for use on tobacco, only a comparatively few have been used to any appreciable extent on a wide-scale basis. The pesticides most used in recent years, or likely to be used in future years, are listed in Table 1 with their acute and chronic toxicities indicated. Many of the compounds listed are applied to the soil prior to planting, to tobacco in plant beds, and to newly set or small tobacco plants. Among these treatments are soil and setting water insecticides (aldrin, heptachlor, chlordane, dieldrin, diazinon, and parathion), systemic insecticides, and herbicides. It seems unlikely that uptake of residues from these treatments, or from soil residues of chlorinated hydrocarbon insecticides which have accumulated from previous foliar treatments, would occur in significant amounts on the harvested tobacco crop. Pesticides applied to larger tobacco plants for control of aphids, leaf-feeding Lepidoptera, Coleoptera, and Orthoptera, as well as fungus diseases and for sucker control include carbaryl, DDT, dieldrin, dimethoate, disyston, endosulfan, endrin, Guthion, malathion, parathion, phosdrin, phosphamidon, TDE, toxaphene, fungicides, and maleic hydrazide. It is this group of pesticides which is most likely to leave a residue because they are applied to tobacco leaves that may be harvested shortly after application.

With the exception of parathion, disyston, phosdrin, phorate, and leaf fumigants, none of the pesticides used extensively on tobacco have great acute toxicity. A number of pesticides in use on tobacco at the present time have tolerances on food less than 1 ppm, but most of these are applied in a manner which precludes any residue problem.

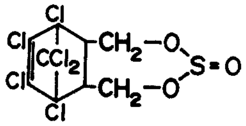
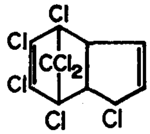
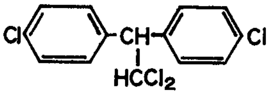
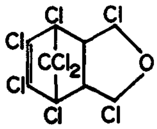
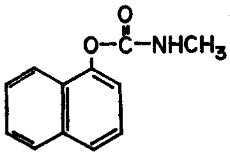
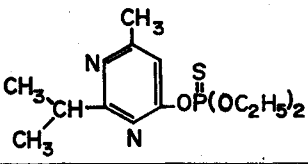
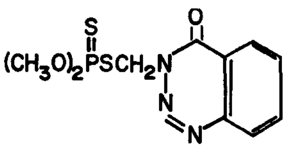
Following entry into a mammalian system, the phosphate and carbamate insecticides are rapidly detoxified and eliminated whereas the chlorinated hydrocarbon insecticides are detoxified more slowly and have a great affinity for storage in fat. The carbamate fungicides are rapidly eliminated in mammalian systems as are the derivatives used as herbicides (56).

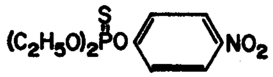
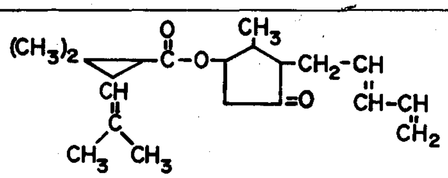
It is important to note that the toxicity of inhaled pesticides has been thoroughly examined but for a very few compounds. Thus, the various regulatory agencies are likely to assume a conservative attitude on pesticides inhaled during smoking until additional data are forthcoming.

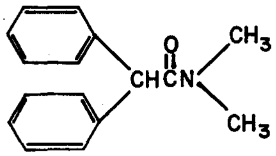
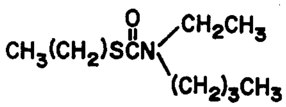
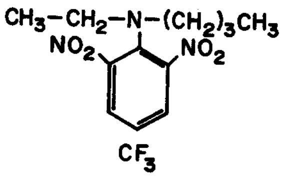
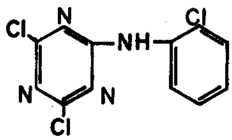
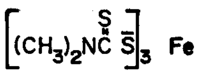
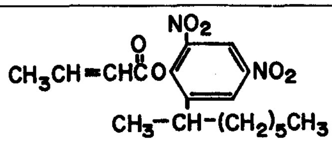
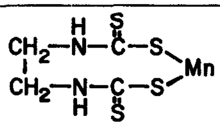
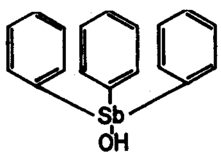
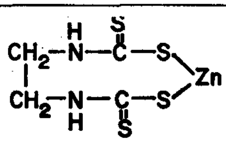
TABLE 1 **Pesticides most commonly used on tobacco and their toxicity to mammals (26, 49, 54, 60, 85)**

Pesticide	Structural formula	Acute toxicity oral LD-50 mg/kg/rat	Chronic toxicity no effect level ppm daily diet	Usual tolerance permitted on food
Insecticides				
Chlorinated				
Aldrin		50–75	0.5*	0.1
DDT		250	5.0	7.0
Dieldrin		40–50	0.5*	0.1

* No effect level not positively established. Figures given are estimates from available literature. NR: No residue tolerance requested at time of registration.

Pesticide	Structural formula	Acute toxicity oral LD-50 mg/kg/rat	Chronic toxicity no effect level ppm daily diet	Usual tolerance permitted on food
Endosulfan		35–70	10.0	2.0
Endrin	Stereoisomer of dieldrin	10–15	–	0.0
Heptachlor		90	0.5*	0.1
TDE (DDD)		3400	10.0	7.0
Telodrin		10	–	NR
Toxaphene	Chlorinated camphene, 67 %	70	10.0	7.0
Carbamates				
Carbaryl (Sevin)		540	200	10.0
Phosphates				
Diazinon		125	1.0	0.75
Dichlorvos	$(CH_3O)_2P(O)OCH{=}CCl_2$	25	15.0	NR
Dimethoate	$(CH_3O)_2P(S)SCH_2NHCH_3$	200	5.0	2.0
Disyston	$(C_2H_5O)_2P(S)SCH_2CH_2SC_2H_5$	3–10	1.0	0.75
Guthion (Azinphosmethyl)		16	5.0	2.0
Malathion	$(CH_3O)_2P(S)-CH(COOC_2H_5)CH_2COOC_2H_5$	1650	100–1000	8.0

Pesticide	Structural formula	Acute toxicity oral LD-50 mg/kg/rat	Chronic toxicity no effect level ppm daily diet	Usual tolerance permitted on food
Parathion		5	1.0	1.0
Phosdrin	$(CH_3O)_2P(=O)OC(CH_3)=CHC(=O)OCH_3$	5	0.8	0.25—1.0
Phorate	$(C_2H_5O)_2P(=S)SCH_2SC_2H_5$	3	–	NR
Phosphamidon	$(CH_3O)_2P(=O)OC(CH_3)=C(Cl)-C(=O)-N(C_2H_5)_2$	15	1.0*	NR
Trichlorfon	$(CH_3O)_2P(=O)CH(OH)CCl$	450	–	0.2
Miscellaneous				
Lead arsenate	$PbHAsO_4$	100	7.0*	7.0
Pyrethrin		200–2600	1000	7.0
Fumigants				
Stored tobacco				
Acrylonitrile	$CH_2=CHCN$	80	–	NR
Dichlorvos	$(CH_3O)_2P(=O)OCH=CCl_2$	25	–	NR
Hydrogen cyanide	HCN	4	100	25–250
Methylbromide	CH_3Br	100	200*	5–240 (as Br)
Soil				
EDB	$BrCH_2CH_2Br$	125	–	10–50 (as Br)
DD	$CHCl=CHCH_2Cl$ + $ClCH_2CHClCH_3$	140	–	NR
Telone	$ClCH=CHCH_2Cl$	300	–	NR

Pesticide	Structural formula	Acute toxicity oral LD-50 mg/kg/rat	Chronic toxicity no effect level ppm daily diet	Usual tolerance permitted on food
Growth Regulators				
Maleic hydrazide		7000	20,000	50
Herbicides				
Diphenamid		700	250	NR
Pebulate		1120	300	NR
Benefin		>2000	–	NR
Fungicides				
Dyrene		2700	5000	10–100
Ferbam		>5700	200	7
Dinocap		1000	500	NR
Maneb		>6000	50*	7–10
Triphenyl tin hydroxide		500	–	NR
Zineb		>5000	500	7

It seems surprising that a problem relating back to 1927 might still serve as a small, but persistent, thorn to the industry. Yet, significant residues of arsenic were reported on cigarette tobacco as late as 1966 (45) with the authors stating "... The amount of arsenic inhaled from cigarettes is still a potential carcinogen to the heavy smoker". Figure 1 presents a summary of arsenic residues on tobacco during the past four decades. A sharp rise in residue levels is evident up to 1954. At this time the various agencies concerned — state, federal, and industrial — made a decided effort to decrease these residues, and the magnitude was appreciably lowered. Although *Holland* and his colleagues persist that arsenic residues on American tobacco are presently at a level of 9 ppm (45), a number of independent studies available to the author conclusively show that arsenic residues do not exceed 2 ppm on cigarettes and more normally are 1 ppm or less. European and Oriental tobaccos have normally been lower in arsenic residues than American tobacco although there are exceptions to this generalization (7, 27, 43, 58, 65, 87). As only 4 to 12 per cent of the arsenic from cigarettes is found in mainstream smoke (7, 24, 33, 46, 47, 75), it is obvious that this source of contamination is no greater than would be expected from naturally occurring arsenic on foods. For example, it has been found that, on an average, natural foods contain 0.6 ppm of arsenic (54) and certain sources, 17 ppm on shrimp, are very high in arsenic (21). For an exhaustive review of arsenic residues on tobacco consult *Wynder* and *Hoffmann* (86). *De Jong's* review (25) concluded that lead (the other constituent of lead arsenate) is of no consequence as a residue hazard on tobacco.

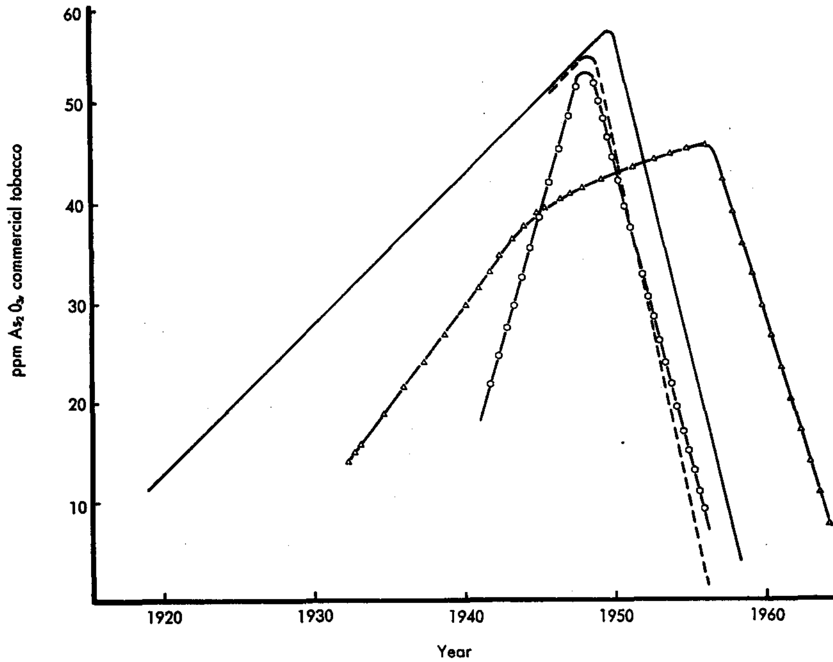


FIGURE 1

Arsenic residues on commercial tobacco (1917–1966)
(7, 36, 45, 48, 83)

RESIDUES OF SYNTHETIC INSECTICIDES

The organic insecticides used to replace arsenicals are applied to the soil, newly set plants, or to the leaves of ripening tobacco. Although appreciable quantities of aldrin, chlordane, heptachlor, diazinon, parathion, dieldrin, and systemic insecticides may be applied to the soil prior to planting and to newly set plants, such applications are expected to leave nil or inconsequential levels on tobacco at the end of the growing season (39, 40). Phosphate, carbamate and chlorinated hydrocarbon insecticides are also used to control insects on larger tobacco plants. The phosphate and carbamate insecticides are dissipated rather quickly by volatilization, hydrolysis, or other weathering factors and excessive residues seldom persist on the green leaf beyond a week. The chlorinated hydrocarbon insecticides are much more persistent, being relatively non-volatile and chemically stable. For example, TDE applied at the rate of 1 pound per acre left residues of 70 ppm one week after treatment whereas the same concentration of carbaryl left residues of only 12 ppm on green tobacco (11, 12).

TABLE 2

Effect of cultural and industrial processes on residues of insecticides applied at purposefully high rates to experimental tobacco (11, 12, 34, 35, 62)

Insecticide	Green (ppm)	Flue-cured (ppm)	Cumulative loss following indicated procedure (%)		
			flue-cured	stemmed and aged	cigarette manufacture
Carbaryl	132	15	89	89	
Dimethoate		0.1	>99		
Endosulfan	102	17	83		
Endrin	101	60	42	45	47
Guthion	356	96*	73	73	
TDE	784	463	41	43	44
Telodrin	17	4	76		
Trichlorfon	213	0.1	>99		

* Guthion plus oxyguthion

Loss of Insecticide Residues from Field Application Through Manufacturing

The data shown in Table 2 are typical of an experiment designed to determine loss of pesticides during the separate events leading up to manufacture. Green tobacco was purposefully treated at excessive levels and immediately harvested to permit subsequent detection of residues. Samples were analyzed following curing and various stages of commercial manufacture.

Flue-curing caused about 40% loss of TDE and endrin, but 76% of telodrin and 83% of endosulfan, two other chlorinated hydrocarbons, were lost as a result of curing. The curing process had a greater effect on carbamate and phosphate residues where 70 to 99% of the pesticides were dissipated. Air-curing has much less effect on residue loss (15% loss of endrin) than flue-curing as would be expected under those milder curing conditions (77). There is little further loss of the residues of TDE, carbaryl, endrin, or Guthion during commercial processing, indicating that the residue on the leaf at the market sales is likely to remain until the tobacco is processed for consumption.

Loss of Residue During Smoking

A logical next step in investigation of the possible dissipation of residues was to ascertain the effect of the 600° to 900° C (20, 32, 82) burning zone of the commercial product both with respect to loss of residues and to possible new pyrolytic products formed. Cigarettes were either made from the high residue tobacco previously discussed or insecticides were directly infused into cigarettes. The cigarettes were smoked on an L & M smoking machine and the mainstream smoke collected from a series of solvents or a cellulose filter. As noted in Table 3, the residues were dissipated to the extent of 95% or greater with the exception of endrin and TDE. Here the loss was about 80%, thus reducing the magnitude of the residue problem by a considerable margin. Breakdown of TDE to TDEE, a less toxic analog of TDE, was appreciable at this stage, and a small amount of the oxygen ana-

TABLE 3

Transfer of insecticides from experimental cigarettes into mainstream smoke (11, 12, 35)

Insecticide	Residue (μg/cigarette)		Loss during smoking (%)
	Cigarette*	Mainstream-smoke	
Carbaryl	150	1.8	99
Endosulfan	100	3.3	97
Endrin	55	10.0	82
Guthion	300	0.6**	99
TDE	440	82.0***	81
Telodrin	100	5.1	95

* Experimentally treated at high levels in field or infused into pesticidefree experimental cigarettes.
** Plus 0.04 oxyguthion.
*** Plus 90 deHCl TDE.

TABLE 4

Insecticide residues (ppm) on grower tobacco sampled at auction sales or from tobacco cultured experimentally which would simulate grower tobacco at time of sale (11, 34, 52, 74, 77).

Area	TDE*			Endrin			Dieldrin	Toxaphene	DDT	
	1958	1960	1962	1958	1960	1962	1962	1957	1962	1967
Flue-cured										
Florida	—	46	21	—	3.6	2.1	—	—	—	—
Georgia	—	43	42	—	1.3	1.8	—	—	—	—
South Carolina	—	36	42	—	2.4	1.2	—	—	—	—
North Carolina	44	27	8	2.2	0.2	1.2	—	7.2	—	—
Virginia	—	11	—	—	0.7	—	—	—	—	—
Dark & burley										
Kentucky	—	30	18	—	—	0.5	0.3	—	—	—
Tennessee	—	17	—	—	1.2	—	—	—	—	—
Cigar wrapper										
Florida	—	—	10	—	—	7.8	—	—	216	125

* Plus DDT (normally 90 % TDE and 10 % DDT on cigarette tobacco) except TDE and DDT reported separately for cigar tobacco.

log of Guthion (which was also suspected to be a product of pyrolysis) could also be detected. In this latter case the pyrolytic product is more toxic than the parent insecticide.

Residues of Insecticides on Commercial, Unmanufactured Tobacco

Up to this point the work reported has been confined to experimental tobacco which was treated at concentrations considerably in excess of recommendation in order to ensure detectable levels during the various phases of processing. Let us now turn our attention to the magnitude and fate of insecticide residues on tobacco produced under normal conditions and processed through the usual commercial steps into the final product.

Table 4 presents data from tobacco collected during annual warehouse sales from a number of tobacco belts in the U. S. The magnitude of the residue from belt to belt or year to year is a reflection of the severity of the insect problem at that time and much variation is to be expected. Surveillance of cigarette tobaccos from 1957 to 1962 from a number of areas show that residues of TDE-DDT (U. S. flue-cured tobacco normally 90 % TDE and 10 % DDT) averaged about 30 ppm, endrin about 1 1/2 ppm. In less comprehensive surveys, residues of dieldrin on burley tobacco were found to be less than 1 ppm, and toxaphene on flue-cured tobacco was 7 ppm. No warehouse surveys on cigarette tobacco have been made since 1962. Residues on cigar wrapper tobacco from the Florida belt are quite high. This is to be expected because it is necessary to treat cigar tobacco on a weekly schedule in that area. The final cigar is composed of only 5 % wrapper, the rest of the tobacco being from areas normally requiring minimal use of insecticides.

TABLE 5

Residue levels (ppm) expected on cured tobacco at time of sale following normal treatment and cultural practices by research stations but where surveys of residues from grower-produced tobacco are lacking (6, 74, 78, 79).

Pesticide	Flue-cured	Cigar wrapper
Dimethoate	0–0.1	—
Disyston	0.5	—
Endosulfan	0.1	20
Malathion	<1.0	—
Parathion	<0.5	3.5
Phorate	0.03	—
Phosdrin	0.3	—
Phosphamidon	0.05	—

Table 5 lists some typical residue levels that would be expected on cured tobacco following treatment at recommended doses and following normal cultural practices by qualified personnel at governmental experiment stations. Surveys for residues of these insecticides have not been made on commercial tobacco, but analyses from the experimental farms should reflect results expected from grower use. The systemic insecticides listed (dimethoate, disyston, phorate, phos-

TABLE 6 **Insecticide residues on manufactured products (4, 11, 34, 44, 52, 69, 70)**

Product	TDE* (ppm)					Endrin (ppm)					Carbaryl (ppm)
	1956	1960	1962	1965	1967	1956	1962	1964	1965	1967	1967
Cigarette	12.4	—	22	32	17	0.2	0.8	1.3	1.5	0.4	<0.3
Cigar	—	17.1	44	11.7	—	—	0.2	—	<0.12	—	—
Pipe tobacco	—	4.8	15	—	—	—	0.3	—	—	—	—
Chewing tobacco	—	4.3	—	—	—	—	—	—	—	—	—
Snuff	—	5.4	20	—	—	—	0.6	—	—	—	—

* Includes TDE, DDT, and associated isomers.

drin, and phosphamidon) are primarily used to protect tobacco against aphid vectors of virus diseases in the Rhodesia and South Africa growing area. These residues would be expected to disappear during smoking or be quickly detoxified by mammalian systems at the minute quantities found on these tobaccos. As endosulfan decomposes when cigarettes are smoked, it would likely also decompose during smoking of cigars. Residues of parathion in fermented cigar wrapper tobacco also seem likely to dissipate during smoking (1), but evidence is lacking. The work of *Noakes* with dimethoate (62) suggests that phosphate insecticides applied to tobacco are of little toxicological significance although his work needs to be confirmed with other compounds.

Residues of Insecticides on Manufactured Tobacco

The magnitude of insecticides on commercial cigarettes has been more extensively followed and more recently monitored (Table 6). The tobacco products used for these studies were purchased on the open market. The quantities of TDE in cigarettes appear to have reached their maximum, and the decline in recent years is attributed to the decreased importance of hornworms on tobacco. Endrin, which was removed from the list of recommended insecticides in 1964 (29, 81, 84), has become increasingly less important as a residue problem in recent years, and it is predicted that this pesticide, like arsenic, will be of academic interest only in the immediate future. Residues of carbaryl, the 2nd most popular tobacco insecticide in the U. S., are below limits of detection in commercial cigarettes. As would be expected, other manufactured forms of tobacco also have appreciable residues of TDE and endrin.

Turning attention to the content of TDE and endrin in smoke of commercial cigarettes (Table 7), it can be noted that the transfer to mainstream smoke closely parallels results from experimental cigarette samples. The loss of TDE during smoking was nearly 90 per cent while that for endrin

TABLE 7 **Residues of insecticides in mainstream smoke of commercial cigarettes (11, 34, 44, 57)**
For identification of decomposition products and analogs see the discussion immediately preceding references.

Cigarette type	No. brands tested	Micrograms / cigarette or "smoked" cigarette										Loss parent compound during smoking (%)
		Cigarette				Mainstream smoke						
		TDE	DDT	DDT analog	Endrin	TDE	DDT	TDEE	DCS	DDT analog	Endrin	
1959 study*												
Regular	7	12.7	—	—	—	1.6	—	1.4	—	—	—	88
King	10	14.7	—	—	—	1.7	—	1.3	—	—	—	88
Filter King	13	10.3	—	—	—	1.6	—	0.6	—	—	—	86
Regular	12	—	—	—	0.19	—	—	—	—	—	0.06	69
1968 study												
Regular	1	11.7	7.8	9.5**	0.0	1.75	0.77	0.81	1.52	1.15***	0.0	87

* TDE and DDT combined in 1959 but DDT averaged less than 10 % of total.
** 4.8 µg o,p-TDE; 1.1 µg TDEE; 3.6 µg o,p-DDT+m,p-TDE.
*** 0.45 µg o,p-DDT; 0.7 µg o,p-DDT+m,p-TDE.

Samples	% of radioactivity found in exhaled smoke
Machine-smoked	4.7
Human, non-inhalers	5.0
Human, inhalers	1.3

TABLE 8

Expulsion of radioactive TDE in mainstream tobacco smoke by non-inhaling and inhaling smokers (10)

was about 70 per cent. Approximately the same quantity of the dechlorinated product, TDEE, was found as the parent product, TDE. The same amount of insecticide was transferred whether the cigarette was a regular, a king, or a filter cigarette. In a recent study (44), the transfer of TDE and DDT into mainstream smoke was also found to be approximately 10 per cent. In addition to TDEE, a new pyrolytic product (4,4'-dichlorostilbene) was reported to be present at about the same magnitude as the parent insecticide. The toxicology of this new pyrolytic product is unknown. Endrin was not detected in that study.

Although the tests just mentioned show conclusively that the chlorinated hydrocarbons were transferred in measurable amounts to mainstream smoke, it is important to determine whether a pesticide is retained during smoking or exhaled. Accordingly, a group of inhaling and a group of non-inhaling smokers consumed cigarettes impregnated with radioactive TDE and exhaled the smoke into a funneled tube connected with suitable collection traps. As shown in Table 8, the non-inhaling smoker expelled essentially all of the pesticide during exhalation. However, the inhaling smokers retained about 70 per cent of the TDE received in the mainstream smoke.

The final step necessary to evaluate the impact of insecticidal residues in mainstream smoke was to determine if the quantities retained in a mammalian system via respiratory intake were treated by the body in a manner similar to intake of oral doses. One preliminary study has been reported which attempts to answer this question. Rabbits selected for their willingness to accept tobacco smoke were placed in *Holland* smoking boxes and cigarettes impregnated with C^{14} TDE were "smoked" in the specially designed apparatus (10). Levels of insecticides in the smoke were calculated at the normal and four times the normal amount from commercial cigarettes. A 45 ml puff of smoke was released into the cages for a duration of two seconds each minute. Rabbits were subjected to the smoke of 20 cigarettes per day for 3 and 6 months exposure period, sacrificed, and the fate of the TDE determined. Table 9 presents the data from this test which suggests that the fate of TDE via inhalation is similar to that via ingestion.

TABLE 9

Residues of TDE in rabbit tissues following exposures to mainstream cigarette smoke from cigarettes containing 48 µg of C^{14}-TDE per cigarette (10)

Tissue	ppm calculated as C^{14}-TDE				Organosoluble components (%)		
	3 months' exposure		6 months' exposure				
	Organo-soluble	Total	Organo-soluble	Total	TDE	deHCl TDE	Unidentified
Avg. 4 tissue fats	0.026	0.027	0.023	0.042	43	56	0
Avg. 7 vital organs	0.010	0.011	0.014	0.062	59	41	0
Avg. 3 respiratory tissues	0.007	0.009	0.006	0.032	33	49	18
Avg. 6 other tissues	0.006	0.008	0.022	0.116	43	57	0
Blood µg/ml		0.011					
Urine µg/ml		0.409					
Feces µg/g		0.007					
(Mainstream smoke)					54	46	

RESIDUES OF OTHER PESTICIDES

Although insecticides are the most potentially hazardous pesticides applied to tobacco, other pesticides have become increasingly important in recent years, and some are applied in large quantities. These materials must also be considered in assessing any residue problem. They will be considered in their approximate order of importance as regards their use on tobacco.

Growth Regulators

Maleic hydrazide is frequently applied to control adventitious buds when tobacco is topped. The high rate of use (2 pounds or more per acre) and stability of this chemical, plus the fact that the lower leaves are full grown and ready for harvest at time of treatment, creates conditions for high residues. Cigarettes made from MH-30 treated tobacco contained 10—30 ppm in 1957 (15, 72), but recent surveys of tobacco from the upper leaf and tip portions of the stalk (not necessarily typical of all commercial tobacco) purchased at warehouse sales indicate residues have been rising in recent years. For example, representative samples of such tobacco from four tobacco belts averaged 44 ppm in 1963, 53 ppm in 1964, 62 ppm in 1965, and 83 ppm in 1966 (14). An extensive survey of maleic hydrazide residues was reported in 1961 (22), but the results are so variable as to be of doubtful significance. It seems likely that MH—30 residues have reached their peak.

One comprehensive study has been reported on the transfer of maleic hydrazide to mainstream smoke (72). Cigarettes containing 100 ppm of C^{14} maleic hydrazide were found to have 23 per cent of the radioactivity transferred to the mainstream smoke. Cigarettes containing 30 ppm were found to have 7 % in the mainstream smoke. Cigarettes containing 10 ppm of maleic hydrazide were smoked without detection of maleic hydrazide in the mainstream smoke. In the cases where maleic hydrazide components were transferred to the mainstream, the author postulated that a large part would be expected to be decomposition products. These products were not identified nor their probable identity suggested.

The question of the hazard of maleic hydrazide residues has been controversial. Whereas one group of investigators exonerates maleic hydrazide as a carcinogen (9), an opposing viewpoint is taken by others (30). The latter study specifically implicates residues in tobacco smoke, among other contaminants, and suggests that the use of maleic hydrazide be greatly decreased where human exposure to these residues is possible.

Pesticides Applied to Tobacco in Storage

Tobacco in storage may be treated with such fumigants as hydrogen cyanide and acrylonitrile-carbon tetrachloride mixtures (for cigarette tobacco in U.S.) and methyl bromide (for cigar tobacco and European cigarette tobacco). Alternate chemicals applied to stored tobacco which are not classified as true fumigants are dichlorvos (DDVP) and pyrethrins. There are no published data concerning the residues to be expected on tobacco or in tobacco smoke following treatment of tobacco in storage (18). Following application to cereal grains, residues of HCN varied between 5—25 ppm following a 30-day posttreatment interval. It is interesting to note that average residues of phosphine, a fumigant presently receiving considerable attention for use on tobacco, were less than 0.01 ppm in wheat similarly treated (30a).

Hydrogen cyanide has been reported in the mainstream smoke of commercial cigarettes at levels of 32—115 micrograms per cigarette (61, 63), while acrylonitrile levels were 0.4—1.5 micrograms per cigarette. The contribution of HCN or acrylonitrile derived from pyrolysis of nitrogenous compounds in tobacco versus the contribution following their use as tobacco fumigants *per se* has not been reported in the literature. One report (50) suggests that the HCN content of tobacco smoke represents little hazard to the normal smoker. Methyl bromide was not detected in the mainstream smoke of commercial U.S. cigarettes (61, 64). Experiments from England reported up to 50 ppm of inorganic bromide to be added by a typical leaf fumigation with methyl bromide (41). Gas chromatographic methods have recently been developed for determining free residual fumigants in foodstuffs (41) and these methods need to be adapted to tobacco before the significance of sorption of fumigants and subsequent retention by tobacco for extended periods can be ascertained.

Pyrethrins and dichlorvos are also applied in a manner which could leave residues on tobacco. As the pyrethrins are very unstable, and have enjoyed the reputation of being among the safest of insecticides for many years, it is extremely unlikely that they pose any residue problem on tobacco. Data available to the author show that less than 1 ppm of DDVP remains on tobacco ready for cigarette manufacture following recommended treatment.

Soil Fumigants

A large portion of the flue-cured tobacco acreage is treated with soil fumigants (such as DD or EDB) for control of nematodes. The tobacco plant accumulates about 0.3 % of chlorine and 0.15 %

of bromine above the normal concentration in the cured leaf (31, 59). From 2.8 to 5.9% of the chlorine and 1.4 to 3.0% of the bromine present in the intact cigarette is transferred to mainstream smoke (59).

Fungicides

Recent outbreaks of blue mold on green field tobacco in Europe were successfully controlled by frequent applications of zineb and maneb. Such treatments left residues at storage ranging from 600 to 4000 ppm (16, 19). About 30 per cent of the maneb disappeared during air curing whereas zineb residues were little affected. When subjected to bulk fermentation about 70 per cent of the residues disappeared. If one calculates the lower expected residue levels (600 ppm) and takes average curing and aging losses, the residue on the final cigarette would exceed 100 ppm.

Studies on the decomposition of zinc ethylenebisdithiocarbamates have shown that the parent compound is completely decomposed during smoking and is absent, as such, in the tobacco smoke. Two main decomposition products, CS_2 and H_2S, were identified in experimental cigarettes at average levels of 115 and 43 µg/cigarette, respectively (17). The concentration of CS_2 in the smoke condensate from cigarettes made from tobacco treated with dithiocarbamate fungicides was 33 µg/cigarette (8). The significance of fungicide-derived CS_2 in tobacco smoke is obscure, but a threshold value of 60 µg/liter has been established where this compound is a manufacturing hazard (2).

Dinocap is used on Rhodesian tobacco for control of white mold, and residues on cured tobacco following recommended use are in the order of 0.1 to 0.7 ppm (79). The fate of the compound during smoking has not been reported.

In recent years brown spot has become an increasingly more important pest late in the season on U.S. flue-cured tobacco. Although not yet serious enough to warrant extensive recommendation of fungicidal treatments, residue studies have begun on three experimental fungicides — Dyrene, maneb, and triphenyl tin hydroxide. Applications of Dyrene and maneb at recommended rates resulted in residues on cured tobacco of 47 and 198 ppm, respectively (55). When tobacco from these tests was stored in 6-month accelerated storage tests, there was no significant decrease in the residues. Cigars injected with 500 ppm of Dyrene and smoked in an artificial smoking apparatus contained 1% of intact Dyrene in the mainstream smoke (3). A decomposition product, o-chloroaniline, was also isolated (5.8%). Applications of triphenyl tin hydroxide resulted in average residue levels of 10 ppm on cured tobacco, and tests are now in progress to determine the fate of such residues during smoking (70a).

Herbicides

Herbicides may be applied to control weeds within a week of the time tobacco is planted. Three herbicides (diphenamid, Pebulate, and Venolate) are registered for use (51), but no data are available concerning residues likely to occur in the cured leaf some three months later. The present culture of tobacco is committed to several cultivations during the early stages of growth, and this mandatory cultivation makes it unlikely that herbicide treatments on tobacco will become important in the foreseeable future.

TOBACCO AND PESTICIDE RESIDUE TOLERANCES

Serious thought has been expressed for the need of the establishment of pesticide tolerances on tobacco in the U.S. (71, 66) and one European country, West Germany (5), has such legislation pending. Therefore, it seems appropriate to discuss this problem in the light of the unique factors one must consider when comparing tobacco with foodstuffs, the standard used for tolerances.

Residue tolerances on foodstuffs are usually established on the "raw agricultural commodity". This is either the fresh food offered at the produce counter or the canned food available after processing, and the comparable tobacco product would be the unsmoked cigarette. Pesticide residues on raw agricultural food commodities are altered little between consumer purchase and consumption.

In the case of pesticide residues on tobacco, however, extensive loss or degradation of pesticides occurs at the consumption phenomenon. The portion of the pesticide transferred to the mainstream smoke is available to the smoker, but the total pesticide in the intact cigarette is not available for consumption. Only after the commodity that is to be consumed (smoke) is inhaled do the tolerance requirements for ingested foodstuffs and ingested smoke appear to be analogous.

Any consideration of the application of tolerances should reflect the loss in tobacco during pyrolysis as well as for the pyrolysis products, both less toxic and more toxic than the parent molecule. For example, combined TDE-DDT residue in a commercial cigarette in 1967 was about 17 ppm, exceeding the tolerance limit of 7 ppm permitted on many foodstuffs. However, the amount of TDE-DDT actually conveyed to the consumer during smoking was about 3.7 ppm, well below tolerances for food.

To avoid the encumbrance of tolerance laws on tobacco, it would seem appropriate to propose that pesticides should not be recommended for use on tobacco when the projected levels of such residues in the mainstream smoke of commercial cigarettes exceed the tolerance established for raw agricultural products, such as leafy vegetables. Such action was taken in 1964 by three recommending bodies (29, 81, 84).

Table 10 is an attempt to summarize how well presently recommended pesticides would fit such a scheme. In some cases there is sufficient data to make accurate predictions. In other cases the data is less reliable, and an estimation is based on the information available from surveys at harvest and from smoking of experimental tobaccos. The insecticides in use today would be expected to fall well within tolerances established on food crops. Although residues of maleic hydrazide may reach 100 ppm on commercial tobacco, extensive loss during smoking causes the residues to fall well below the 50 ppm permitted on food. Parent fungicides are decomposed during smoking or are well below tolerances prior to manufacture. The magnitude and significance of the decomposition products of ethylenebisdithiocarbamates, CS_2 and H_2S, requires clarification before an evaluation can be made. Extremely high levels of fungicides should be avoided until more data are available.

At this point it seems important to reflect on the occurrence of natural and pyrolytically-produced toxic substances in tobacco and tobacco smoke which are unrelated to use of pesticides. These compounds, the most important of which are nicotine, HCN, and CS_2, must also be considered if tolerances are adapted to tobacco. Two milligrams of nicotine are present in cigarettes, and approximately 1,000 micrograms are absorbed via the mainstream smoke. Although a large volume of literature indicates that mammals can tolerate nicotine in subchronic doses without ill effects for long periods of time and the Surgeon General's committee (73) stated that the nicotine inhaled during smoking "probably does not represent a significant health hazard", the usual tolerance for

TABLE 10

Comparison of pesticide tolerances on food with residues expected in cigarette smoke following treatment of tobacco at recommended rates and time intervals and assuming normal cultural and manufacturing procedures.

The pesticides listed are those most frequently used on tobacco (6, 12, 17, 34, 44, 62, 70, 72, 79, 61, 63).

Pesticide	Anticipated on treated tobacco (ppm or µg/smoked cigarette)		Tolerance or "expected" tolerance*** (ppm)	Levels actually found in mainstream smoke of commercial cigarettes (µg/smoked cigarette)
	Flue-cured	In smoke		
Insecticides				
TDE	35	7.0	7	1.7 (1959); 3.67 (1968)
Endrin	4.2	1.2	zero	0.06 (1959); 0 (1968)
Carbaryl	1.4	0.01	10	<0.3
Guthion	1.8	0.001	2	–
Dimethoate	0.1	0	2.0	–
Parathion	0.5	0	0.75	–
Growth regulators				
Maleic hydrazide	83	19	50	–
Fungicides				
Dinocap	0.7	<0.5	10	–
Zineb	100*	0**	7	–
Fumigants and other materials used on stored tobacco				
HCN	–	ukn	25	>30
DDVP	–	<1.0	2.0	–
Methyl bromide	–	ukn	25	–
Pyrethrins	–	<1.0	3.0	–

* After fermentation.
** 33 µg/cigarette of the decomposition product, CS_2, expected.
*** Tolerances based on U. S. Pure Food and Drug Laws and other countries may be more or less conservative in their tolerance laws.

nicotine on food is 2 ppm. Obviously this is an impossibly realistic tolerance for tobacco. The content of HCN in tobacco smoke from unfumigated tobacco is also above levels permitted on some foods. If these, and similar anomalies, are not given consideration prior to establishment of tolerances, legislation might be enacted which would be impossible to obey. Although there are established limits for many gaseous compounds, these are ascribed for continuous exposure in a confined area, a situation not necessarily applicable to smoking. Small quantities of toxicants administered slowly can often be detoxified and excreted by the mammalian system without ill effect. Many compounds in the Krebs Cycle, for example, would be considered toxic if introduced to the system with food.

It is of interest at this point to compare the daily intake of a common pesticide from food versus that from tobacco. The only comprehensive evaluation of the daily intake from cigarette smoke was made in 1959 (11) at which time the one pack per day inhaling smoker would receive about 0.03 milligrams of TDE plus DDT. Applying an appropriate factor for a survey of 6 bands in a 1967 study (70), the average daily intake would be 0.04 milligrams per day. In a study based on one brand of cigarettes in 1968 (44), the average daily intake would be 0.07 milligrams per day. The amount of DDT found in total diet studies of food (Market Basket Survey) in 1964 in the U.S. was 0.04 milligrams per day (23). Both tobacco and food contain quantities in excess of the 0.01 milligrams per day considered to be safe by the very conservative estimate of the World Health Organization (85) but are in general agreement with the acceptable daily intake figures (0.04 mgs/day) of the U.S. Food and Drug Administration. Nonetheless, scientists serving the industry must keep abreast of this problem and continuously strive to reduce these residues. A number of means for reducing pesticide residues which have been investigated, or are presently under investigation, are listed below:

Means of reducing and minimizing residues:

1. Recommendations made by appropriate recommending agencies should never be exceeded by growers.
2. Adherence to economic threshold levels before treatment preventing growers from making blanket applications when not necessary (53).
3. Placement of pesticide to minimize drift to parts of plant not requiring protection and timing of applications for maximum dissipation before harvest (37, 38).
4. Continued search for pesticides more easily decomposed during curing and smoking and more easily detoxified in mammalian system.
5. Resistant varieties-insects and diseases (42, 76).
6. Biological control agents (13, 67).

Among the residue problems on tobacco which presently require attention are:

1. Continued monitoring of manufactured tobacco products.
2. Isolation, identification, and toxicological evaluation of the pesticide components found in mainstream and sidestream smoke.
3. Contribution of the HCN and CS_2 level of mainstream smoke from application of fumigants and fungicides.
4. Retention of pesticide residues following use of cigar, pipe, snuff, and chewing tobaccos.
5. Comparison of residues of DDT-TDE in fat of smokers and nonsmokers.

SUMMARY

Residues of inorganic insecticides used on tobacco have decreased to the extent that they are primarily of academic interest only.

Organic pesticides used for control of pests, including sucker growth, can often be detected at high levels during the early phases in the culture of tobacco due to the large surface-to-weight ratio characteristic of leafy products. Residues of 100 ppm are not uncommon for stable pesticides on green tobacco ready for harvest and even pesticides which normally dissipate quickly after treatment, as parathion, may exceed 4 ppm following normal treatment. During the flue-curing process, from 40—99 per cent of the residues disappear. Air-curing is much less effective in destroying the residues as would be expected. During smoking of cigarettes 80—90 per cent of such stable compounds as the chlorinated hydrocarbons is decomposed or transferred to the sidestream

smoke whereas less stable pesticides, as phosphate insecticides or carbamate fungicides, are normally detected in mainstream smoke at levels less than 5 per cent of that present in the cigarette before smoking. The fate of TDE, the most common insecticide found in mainstream cigarette smoke from commercial cigarettes, appears to follow the same route of degradation in mammalian systems whether inhaled or introduced orally.
The levels of pesticides found in mainstream smoke of commercial cigarettes, or expected from recommended treatment, are below the tolerance ascribed on food by several countries. However, additional research is needed to clarify the contribution of applied pesticides from the same compounds produced pyrolytically during cigarette consumption.
Continuous surveillance of manufactured tobacco for pesticide residues, increased research on the isolation and identity of decomposition products in mainstream smoke, and augmentation with non-pesticidal or decreased pesticidal methods should be encouraged.

ZUSAMMENFASSUNG

Die Verwendung anorganischer Insektizide im Tabakanbau ist auf ein so geringes Maß zurückgegangen, daß ihnen nur noch akademisches Interesse zukommt.
Die organischen Pflanzenschutzmittel und die Mittel zur Kontrolle des Geizenwachstums können in den frühen Phasen des Wachstums der Tabakpflanze vielfach in größeren Mengen nachgewiesen werden. Dies liegt an der relativ großen Oberfläche der Tabakblätter im Verhältnis zu ihrem Gewicht. Restmengen von 100 ppm sind bei beständigen Pflanzenschutzmitteln auf grünem Tabak kurz vor der Ernte nicht ungewöhnlich, und selbst Pflanzenschutzmittel wie das Parathion, die nach der Anwendung normalerweise schnell verschwinden, können nach normaler Behandlung in Resten von mehr als 4 ppm vorliegen. Während der Röhrentrocknung vermindern sich die Restmengen um 40—99 %. Die Lufttrocknung bewirkt erwartungsgemäß einen viel geringeren Abbau der Rückstände. Während des Rauchens von Cigaretten werden von so beständigen Verbindungen wie den chlorierten Kohlenwasserstoffen 80—90 % zersetzt, oder sie gehen in den Nebenstromrauch. Die nicht so beständigen Pflanzenschutzmittel wie die Phosphor-Insektizide oder die fungiziden Karbamate können im Hauptstromrauch normalerweise in Anteilen von weniger als 5 % der in der ungerauchten Cigarette vorliegenden Reste nachgewiesen werden. Das TDE, ein Insektizid, das im Hauptstromrauch handelsüblicher Cigaretten am häufigsten gefunden wird, unterliegt im Organismus von Säugetieren nach Inhalation dem gleichen Abbau wie nach oraler Applikation.
Die Reste von Pflanzenschutzmitteln, die im Hauptstromrauch handelsüblicher Cigaretten nachzuweisen oder nach einer empfohlenen Art der Anwendung zu erwarten sind, liegen quantitativ unter den Toleranzen, die in mehreren Ländern für Lebensmittel festgelegt sind. Hingegen sind weitere Untersuchungen erforderlich, um zu klären, welche Bedeutung den Abbauprodukten zukommt, die beim Abrauchen von Cigaretten durch Pyrolyse aus diesen Verbindungen entstehen.
Die ständige Kontrolle von Tabakerzeugnissen auf Reste von Pflanzenschutzmitteln sowie Forschungsarbeiten zur Isolierung und Identifizierung der Abbauprodukte im Hauptstromrauch sollten weiter ausgebaut werden. Außerdem sollten verstärkt Methoden des Pflanzenschutzes ohne oder mit verminderter Verwendung chemischer Mittel entwickelt werden.
Nachtrag: Nach der Einreichung dieses Manuskriptes verabschiedete die Arbeitsgruppe Entomologie der 22. Tobacco Workers' Conference (Asheville, N. C., 22. — 24. Juli 1968) eine Entschließung, das DDT von der Liste der Insektizide zu streichen, die für den Feldanbau von Tabak empfohlen werden.

RÉSUMÉ

Les résidus d'insecticides inorganiques utilisés sur le tabac ont diminué de manière à ne présenter qu'un intérêt académique.
Les pesticides organiques appliqués pour la lutte contre les parasites du tabac, y compri l'ébourgeonnement, peuvent souvent se trouver en doses importantes durant les premières phases de la culture du tabac, en raison de la valeur élevée du rapport surface/poids qui caractérise les parties feuillues. Sur le tabac vert, au moment de la récolte, des taux de 100 ppm de résidus ne sont pas rares pour les pesticides stables, et même les taux de pesticides, tels que le parathion, qui normalement se dissipent vite après le traitement, peuvent dépasser 4 ppm à la suite de traitements normaux. Au cours du flue-curing, de 40 à 99 % des résidus de pesticides disparaissent. Comme il

est à supposer, l'air-curing est beaucoup moins efficace pour la destruction des résidus. Pendant la combustion de la cigarette, 80—90 % des composés stables tels que les hydrocarbures chlorés sont décomposés ou transférés dans le courant secondaire de fumée, alors que les combinaisons moins stables tels que les pesticides du type ester phosphorique ou les fongicides du type carbamate peuvent normalement être retrouvés dans le courant principal de fumée en doses inférieures à 5 % de la quantité présente dans la cigarette avant le processus de fumage. Le TDE pesticide le plus communément trouvé dans le courant principal de fumée des cigarettes du commerce, paraît suivre le même processus de dégradation dans l'organisme des mammifères, qu'il soit inhalé ou introduit par la voie digestive.
Les taux de pesticides trouvés dans le courant principal de fumée des cigarettes du commerce ou à attendre à la suite du traitement recommandé sont au-dessous des tolérances fixées pour les aliments dans de nombreux pays. Il est toutefois nécessaire de poursuivre les travaux de recherche afin que la contribution apportée par les produits de décomposition se formant par pyrolyse à partir des pesticides appliqués durant la consommation de la cigarette soit éclaircie.
On devrait encourager la surveillance continue de la teneur en résidus de pesticides du tabac manufacturé, les études approfondies sur l'isolement et l'identification de produits de décomposition présents dans le courant principal de fumée et l'élaboration de méthodes de lutte contre les parasites animaux et végétaux du tabac qui ne se servent pas ou dans une faible mesure seulement de l'emploi de composés pesticides chimiques.

Addendum

Subsequent to submission of this manuscript, the Entomology Section of the 22nd *Tobacco Workers' Conference* (Asheville, N. C., July 22—24, 1968) passed a resolution to remove DDT from the list of recommended insecticides for use on field-grown tobacco.

Identity of abbreviations used for decomposition products of DDT and TDE:
DDT and TDE isomers include the p,p'- (most toxic form), o,p- and m,p-forms. Both of these compounds may be dechlorinated to their respective ethylenic derivatives. Both the ethylenic derivative of TDE, designated as TDEE (1-monochloro-2,2-bis[p-chlorophenyl]ethylene), and DDT, designated as DDE (2-dichloro-2,2-bis[p-chlorophenyl]ethylene), have been isolated from tobacco smoke (44). They are both less toxic than the parent insecticide. Another decomposition product which appears in tobacco smoke in relatively high concentrations is 4,4-dichlorostilbene or DCS. The toxicology of this compound is not known.

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Acknowledgment

Supported by PHS Grants EF 00158, ES 00044, and the Council for Tobacco Research. The cooperation of the major tobacco manufacturing companies and the Entomology Section, Tobacco Workers' Conference, is gratefully acknowledged. Published as Paper 2705 of the Journal Series of the North Carolina Agricultural Experiment Station, Raleigh, North Carolina.

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