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INDIAN SCENARIO OF PESTICIDE RESIDUES ON TOBACCO AND ITS WAY FORWARD TOWARDS PRECISE DETECTION IN COMPLIANCES TO TRADE

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When used as intended—most commonly in cigarettes—tobacco is generally inhaled into the body. However, because it is not a food, tobacco is regulated as a nonfood crop with regard to pesticide residues. That is, no residue limits are established or monitored for pesticides approved for use on tobacco, as is done for foods. While the regulation of pesticide residues on tobacco is limited because it does not include pesticides approved for use on this crop, U.S. Department of Agriculture (USDA), Environmental Protection Agency (EPA) tests tobacco for residues of 20pesticides not approved for domestic use on tobacco, primarily for purposes of trade equity. Because many of the tested pesticides are knownto harm humans and the environment, the testing program helpsminimize the public's exposure to some highly toxic pesticides. The regulatory testing program would beimproved by assessing the current universe of pesticides not approved foruse on tobacco and determining whether an update to its program iswarranted.

1. INTRODUCTION

Tobacco is a high-value, pesticide-intensive crop. That is, tobacco is the nation's ninth highest valued crop, and in terms of the amount of pesticideapplied per acre, tobacco ranks sixth-behind potatoes, tomatoes, citrus, grapes, and apples. Although pesticides play a significant role in increasing production of tobacco, food, and other crops by reducing the number of crop-destroying pests, exposure to pesticides can harm humans. The potential for harm is related to both the amount of a substance a person is exposed to-the dose-and the toxicity of the chemical. For example, small doses ofaspirin can be beneficial to people, but at very high doses, this common medicine can be deadly. In general, to control tobacco stem borer, bud worm, whitefly and sucking pests and to control sucker growth different crop protection chemicals *viz.,* imidacloprid, thiamethoxam, decanol, pendimethalin, new generation pesticides like emamectin benzoate, flonicamid, flumetralin, chlorantraniliprole etc. used in tobacco crop.

Furthermore, in some individuals, even at verylow doses, aspirin may be lethal (Jebet et al., 2018, Kumari et al., 2004). The age and health status of an individualcan also affect the potential for harm. Children may be more susceptible toharm because, for example, they eat more food, drink more water, andbreathe than adults per pound body weight, resulting in greaterexposure. Generally, assessments of dose and response involve considering the dose levels at which adverse effects are observed in test animals and using these dose levels to calculate an equivalent dose in humans.

Apart from this, the COVID-19 pandemic has added another factor to the situation by pushing up costs for farmers while reducing income. The pandemic has also made it harder to get farm labour and more complicated to get crops to a functioning market.

The residue levels in tobacco leaves are expected todecline up to harvest, during drying, and when the leaves are further processed. Additional pesticides may also be applied to the finished product and residue levels may remain present even when the tobacco is burned.

Varying residue levels may be found in the tobacco, and also in the next step when the tobacco is burned (GAO 2003). As a result, human exposure to pesticide residues on tobacco may occur when residues remaining in cigarette smoke are inhaled.

While much is known about the significant health risks of using tobacco products itself (Kurgat et al. 2016), limited information exists on the extent to which the use of pesticides on tobacco may increase the health risks associated with tobacco consumption (GAO 2003).

At national and international level, tobacco is one of the crops which receives higher loads of pesticides (Muiño-García et al. 2016; Hernández et al. 2016). In our previous study under publication (Review Round 2, in the *Spanish Journal of Agricultural Research*), it was found that tobacco was one of the crops that received the highest amounts of pesticides. Despite knowing which pesticides that are used in tobacco production and their quantity, the level of those residues present in the tobacco leaves and their occurrence in the smoke is unknown.

Against this background, this review considers a holistic scenario regarding the export from different countries like European Union (EU), United states, Brazil including India. Member States to developing countries of some pesticides that have been banned from use within the European Union (EU), because it has recognised the hazardous nature of those pesticides. As for example organochlorine and organo phosphate pesticide, specifically, DDT which are banned globally, whereas, malathion banned by EU, in India it is verge to ban in near future. However, it remains possible to export pesticides that are currently banned from use within the different countries. Four of the top ten destinations for this category of pesticide are countries in Latin America, led by Brazil. Although less than 5 % of pesticide sales currently go to Africa, the use of pesticides is growing sharply, especially in West Africa since the arrival of a major new crop pest, the Fall armyworm, in 2016.

2. Residue levels of pesticides across different countries

2.1. Regulatory guidelines across different continent

U.S. Department of Agriculture has implemented the Dairy and Tobacco Adjustment Act, in part, by setting 15 residue limits (maximum allowable concentrations) covering 20pesticides currently not approved for use on tobacco in the United States that the agency believed were used in other countries. Most of the pesticides USDA regulates, such as DDT and toxaphene, are organochlorine pesticides. As discussed earlier, organochlorine pesticides persist in the environment and accumulate in the bodies of humans andanimals, and many are highly toxic—a number of them have been banned for these reasons. Of the 15 residue limits, 11 pertain to individual pesticides, while 4 address combinations of two or more pesticides. Forexample, aldrin and dieldrin are summed because dieldrin is the primarydegradation product of aldrin. Table 1 lists the residue limits included in USDA's testing program, with the 12 organochlorine pesticides highlighted. As indicated in the table, methoxychlor is the only organochlorine pesticide included in USDA's testing program that is currently approved for other uses in the United States, such as on foodcrops.USDA does not currently regulatepesticide residues of lindane because it was still approved for tobaccowhen USDA last reevaluated the regulated pesticides. Other pesticides, such as trichlorfon and diazinon, are also potential candidates for regulation, as they are no longer approved for use on tobacco in the United States but may still be utilized in other countries..Table 2 shows that some countries that set limits for pesticides used on tobacco have established them for trichlorfon and diazinon—one of the leading causes of acuteinsecticide poisoning for humans. However, since the USDA has not updated the list of regulated pesticide residues it monitors, the testing program might overlook certain pesticides with similar properties to those currently tested, which could still be in use in other countries, viz. Brazil, China, South Africa etc. Tobacco and pesticide expertswith whom we spoke agreed that periodic reevaluations of the regulated pesticides would be appropriate. Furthermore, two of these experts—atoxicologist who has measured residues on tobacco for many years and a former government official who now represents tobacco producers—told them that many of the pesticides USDA currently regulates, particularly the organochlorine pesticides, warrant continued inclusion in the testing program because they are persistent in the environment, accumulate in the body, and continue to be used on crops overseas.

Table 1: USDA's Residue Limits for Pesticides on Tobacco

Pesticide (organochlorine pesticides in bold)	Residue limit (ppm)	Approved for non-tobacco use(s)
Chlordane	3.0	No
Dibromochloropropane (DBCP)	1.0	No
Dicamba	5.0	Yes
Endrin	0.1	No
Ethylene dibromide (EDB)	0.1	No
Formothion	0.5	No
Hexachlorobenzene (HCB)	0.1	No
Methoxychlor	0.1	Yes
Toxaphene	0.3	No
2,4-D	5.0	Yes
2,4,5-T	0.1	Yes
Sum of aldrin and dieldrin	0.1	No
Sum of cypermethrin and permethrin	3.0	Yes
Sum of DDT, TDE, and DDE	0.4	No
Sum of heptachlor and heptachlor epoxide	0.1	No

To determine the extent to which EPA, USDA, and other federal agencies regulate and monitor pesticide residues on tobacco, we met with cognizant officials and reviewed authorizing legislation, regulations, and documentation on how programs related to pesticide residues on tobacco are implemented. In addition, Federal body analyzed USDA data on tobacco production, imports, and residue-testing results. They also interviewed academic and tobacco industry experts and reviewed residue data collected by North Carolina State University. To provide information on other countries that have adopted regulatory limits on pesticide residues, they reviewed articles by academic experts on the international regulation of pesticides on tobacco. They provide information on three major importers of U.S. tobacco—Germany, Italy, and Spain—as examples of regulatory approaches in other countries, focusing on the residue limits they set. They did not examine how, or the extent to which, these countries monitor or enforce their pesticide residue limits. They updated and clarified the information on the three countries' residue limits provided in the articles with information from the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA), an International Tobacco Research Organization, and officials responsible for oversight of pesticides and tobacco in Germany and Spain. To identify countries that import U.S. tobacco, we extracted data from the United States International Trade Commission's interactive tariff and trade database on the countries that received U.S. flue-cured and burley tobacco from 1996 through 2020.

Several countries that are major importers of U.S. tobacco have adopted regulations for specific pesticide residues on various forms of tobacco. For example, Germany's residue limits (maximum residue levels) apply tofinished products, such as cigarettes, whereas limits in Italy and Spain generally apply to tobacco leaf. Although they have somewhat different regulatory approaches to pesticides on tobacco, Germany, Italy, and Spain differ from the United States in that they regulate residues of pesticides approved for use on tobacco in addition to regulating some residues of pesticides not approved for use on tobacco.

Guidance Residue Levels (GRLs) have been developed by the CORESTA Agro-Chemical Advisory Committee (ACAC), to provide guidance to tobacco growers and those in the tobacco industry interested in Crop Protection Agents (CPAs) application and the implementation of Good Agricultural Practice(GAP) in tobacco production. GRLs are intended to assist with the interpretation and evaluation of CPA residue testing results and serve as an indicator that GAP is being implemented. In 2003 GRLs were developed for 99 CPAs, which may be included in the range of CPA residue analysis routinely offered by the major testing laboratories. The list is revised periodically as needs demand and now covers 116 CPAs (CORESTA 2021). As a result, it contains additional compounds and changes to some of those in the original list following full reviews of all compounds in the light of continuing changes in CPA registrations, labels, regulations and agricultural practices, and based also on improvements in analytical methods, knowledge of degradation patterns and information about residues. GRLs do not replace requirements to comply with regulations, neither on the use of CPAs, norwith regard to residue levels that may be detected (Table

Table 2: Residue Limits Adopted by Germany, Italy, and Spain for pesticides commonly used on Tobacco

Pesticide	Residue limits (ppm) country wise		
	Germany[a]	Italy[b]	Spain[c]
Acephate	d	1.5	d
Aldicarb	10.0	0.6 (green)3.0 (cured)	5.0
Benefin	d	0.01	0.02
Carbaryl	3.0	3.0	0.1
Carbofuran	20.0	0.1	10.0
Chlorpyrifos	d	0.2	0.05
Diazinon	1	d	0.02
Dichloropropene	d	d	0.05
Diphenamid	1.5	0.1	5.0
Disulfoton	1.0	0.4	d
Endosulfan	20.0	1.0	d
Ethephon	d	16.0 (green)80.0 (cured)	d
Ethoprop	3.0	0.02	0.02
Fenamiphos	15.0	0.1	0.02
Flumetralin	20.0	2.0 (green)10.0 (cured)	5.0
Fonophos	1.0	0.05	d
Imidacloprid	d	10.0 (green)50.0 (cured)	5.0
Isopropalin	0.5	0.02	d
Malathion	3.0	0.5	0.5
Maleic hydrazide	80.0	80.0	80.0
Mancozeb	50.0	2.0 (green)10.0 (cured)	0.05
Metalaxyl	d	1.0	3.0
Methidathion	1.0	d	d
Methomyl	2.0	d	d
Methyl bromide	d	d	20.0
Napropamide	0.1	0.1	0.05
Pebulate	0.5	d	0.05
Pendimethalin	d	d	0.05
Sethoxydim	d	0.05	d
Trichlorfon	1.0	0.1	0.1

[a]Residue limit on finished products.
[b]Residue limit on green tobacco if not otherwise specified.
[c]Residue limit on dried tobacco.
[d]Country has not adopted limits for this pesticide

Table 3: GRL levels set by CORESTA (followed by Asian, African, Brazil, China, countries)

No. (ppm)	CPA Residue definition	GRL	
1	2,4,5-T	0.05	2,4,5-T
2	2,4-D	0.2	2,4-D
3	Acephate	0.1	Acephate
4	Acetamiprid	3	Acetamiprid
5	Acibenzolar-S-methyl	5	Acibenzolar-S-methyl
6	Alachlor	0.1	Alachlor
7	Aldicarb	0.5	sum of Aldicarb, Aldicarbsulfoxide and Aldicarb sulfone,expressedasAldicarb
8	Aldrin+Dieldrin	0.02	Aldrin+Dieldrin
9	Azinphos-ethyl	0.1	Azinphos-ethyl
10	Azinphos-methyl	0.3	Azinphos-methyl
11	Azoxystrobin[h]	16	Azoxystrobin
12	Benalaxyl	2	Benalaxyl
13	Benfluralin	0.06	Benfluralin
14	Benomyl[a]		sum of Benomyl, Carbendazim,and Thiophanate-methylexpressedasCarbendazim
15	Bifenthrin	3	Bifenthrin
16	Bromophos	0.04	Bromophos
17	Butralin	5	Butralin
18	Camphechlor(Toxaphene)	0.3	Camphechlor (mixture ofchlorinatedcamphenes)
19	Captan	0.7	Captan
20	Carbaryl	0.5	Carbaryl
21	Carbendazim[a]	2	sum of Benomyl, Carbendazim,and Thiophanate-methylexpressedasCarbendazim
22	Carbofuran	0.5	sum of Carbofuran and 3-Hydroxycarbofuran expressed asCarbofuran
23	Chinomethionat	0.1	Chinomethionat
24	Chlorantraniliprole	14	Chlorantraniliprole
25	Chlordane	0.1	sum of cis-Chlordane and trans-Chlordane
26	Chlorfenvinphos	0.04	sumof(E)-Chlorfenvinphosand(Z)-Chlorfenvinphos
27	Chlorothalonil	1	Chlorothalonil
28	Chlorpyrifos	0.5	Chlorpyrifos
29	Chlorpyrifos-methyl	0.2	Chlorpyrifos-methyl
30	Chlorthal-dimethyl	0.5	Chlorthal-dimethyl
31	Clomazone	0.2	Clomazone
32	Cyantraniliprole[h]	18	Cyantraniliprole
33	Cyfluthrin	2	Cyfluthrin(sumofallisomers)
34	Cyhalothrin	0.5	Cyhalothrin(sumofallisomers)
35	Cymoxanil	0.1	Cymoxanil
36	Cypermethrin	1	Cypermethrin (sum of allisomers)
37	DDT	0.2	sumofo,p'-andp,p'-DDT,o,p'- and p,p'-DDD (TDE), o,p'- andp,p'-DDEexpressedasDDT
38	Deltamethrin[b]	1	sum of Deltamethrin andTralomethrin expressed asDeltamethrin
39	Demeton-S-methyl	0.1	sum of Demeton-S-methyl,Oxydemeton-methyl (Demeton-S-methyl sulfoxide) andDemeton-S-methyl sulfoneexpressedasDemeton-S-methyl

40	Diazinon	0.1	Diazinon
41	Dicamba	0.2	Dicamba
42	Dichlorvos[c]	0.1	sum of Dichlorvos, NaledandTrichlorfon expressed asDichlorvos
43	Dicloran	0.1	Dicloran
44	Difenoconazole[h]	12	Difenoconazole
45	Diflubenzuron	0.1	Diflubenzuron
46	Dimethoate[d]	0.5	sum of Dimethoate andOmethoate expressed asDimethoate
47	Dimethomorph	2	sum of (E)-Dimethomorph and(Z)-Dimethomorph
48	Disulfoton	0.1	sum of Disulfoton, Disulfotonsulfoxide, and DisulfotonsulfoneexpressedasDisulfoton
49	Dithiocarbamates(as CS2) [e]	5	Dithiocarbamates expressed asCS2
50	Endosulfans	1	sum of alpha- and beta-isomersand Endosulfan-sulphateexpressedasEndosulfan
51	Endrin	0.05	Endrin
52	Ethoprophos	0.1	Ethoprophos
53	Famoxadone	5	Famoxadone
54	Fenamidone [h]	3	Fenamidone
55	Fenamiphos	0.5	sum of Fenamiphos, Fenamiphossulfoxide and FenamiphossulfoneexpressedasFenamiphos
56	Fenitrothion	0.1	Fenitrothion
57	Fenthion	0.1	sum of Fenthion, Fenthionsulfoxide and Fenthion sulfoneexpressedasFenthion
58	Fenvalerate	1	Fenvalerate (sum of all isomers including Esfenvalerate)
59	Fluazifop-butyl	1	Fluazifop-butyl(sumofallisomers)
60	Flubendiamide[h]	18	Flubendiamide
61	Flumetralin	5	Flumetralin
62	Fluopyram[g]	5	Fluopyram
63	Flupyradifurone[i]	21	Flupyradifurone
64	Folpet	0.2	Folpet
65	HCH(á-,â-,ã-)	0.05	HCH(á-,â-,ã-)
66	HCH(ã-)(Lindane)	0.05	HCH(ã-)(Lindane)
67	Heptachlor	0.02	sumofHeptachlorandtwoHeptachlor epoxides (cis-andtrans-)expressedasHeptachlor
68	Hexachlorobenzene	0.02	Hexachlorobenzene
69	Imidacloprid	5	Imidacloprid
70	Indoxacarb	6	SumofSisomer+Risomer
71	Iprodione	0.5	sumofIprodione and N-3,5-dichlorophenyl-3-isopropyl-2,4-dioxoimidazolyzin-1-carboxamideexpressedasIprodione
72	Malathion	0.5	Malathion
73	Maleichydrazide	80	Maleic hydrazide (free andboundedform)
74	Metalaxyl	2	sum of all isomers includingMetalaxyl-M /Mefenoxam
75	Methamidophos	1	Methamidophos
76	Methidathion	0.1	Methidathion
77	Methiocarb	0.2	sum of Methiocarb, Methiocarbsulfoxide, and Methiocarb sulfoneexpressedasMethiocarb
78	Methomyl[f]	1	sum of Methomyl, Methomyl-oxim, and Thiodicarb expressed as Methomyl

79	Methoxychlor	0.05	Methoxychlor
80	Mevinphos	0.04	Mevinphos (sum E and Zisomers)
81	Mirex	0.08	Mirex
82	Monocrotophos	0.3	Monocrotophos
83	Naled[(c)]		sum of Dichlorvos, Naled, andTrichlorfon expressed asDichlorvos
84	Nitrofen	0.02	Nitrofen
85	Omethoate[(d)]		sum of Dimethoate and Omethoate expressed as Dimethoate
86	Oxadixyl	0.1	Oxadixyl
87	Oxamyl	0.5	Oxamyl
88	Parathion(-ethyl)	0.06	Parathion
89	Parathion-methyl	0.1	Parathion-methyl
90	Pebulate	0.5	Pebulate
91	Penconazole	1	Penconazole
92	Pendimethalin	5	Pendimethalin
93	Permethrin	0.5	Permethrin(sumofallisomers)
94	Phorate	0.05	Phorate
95	Phosalone	0.1	Phosalone
96	Phosphamidon	0.05	Phosphamidon (sum of E and Zisomers)
97	Phoxim	0.5	Phoxim
98	Piperonylbutoxide	3	Piperonylbutoxide
99	Pirimicarb	0.5	Pirimicarb
100	Pirimiphos-methyl	0.1	Pirimiphos-methyl
101	Profenofos	0.1	Profenofos
102	Propamocarb[(h)]	13	Propamocarb
103	Propoxur	0.1	Propoxur
104	Pymetrozine	1	Pymetrozine
105	Pyrethrins	0.5	sum of Pyrethrins1, Pyrethrins2, Cinerins1, Cinerins2, Jasmolins 1 and Jasmolins 2
106	Tebuconazole[(h)]	18	Tebuconazole
107	Teflubenzuron[(h)]	3	Teflubenzuron
108	Tefluthrin	0.1	Tefluthrin
109	Terbufos	0.05	sum of Terbufos, Terbufos sulfoxide and Terbufossulfone expressed as Terbufos
110	Thiamethoxam	5	Thiamethoxam
111	Thiodicarb[(f)]		sum of Methomyl, Methomyl-oxim, and Thiodicarb expressed as Methomy l
112	Thionazin	0.04	Thionazin
113	Thiophanate-methyl[(a)]		sum of Benomyl, Carbendazim,and Thiophanate-methyl expressed as Carbendazim
114	Tralomethrin[(b)]		sum of Deltamethrin and Tralomethrin expressed as Deltamethrin
115	Trichlorfon[(c)]		sum of Dichlorvos, Naled, and Trichlorfon expressed as Dichlorvos
116	Triflumuron[(h)]	4	Triflumuron
117	Trifluralin	0.1	Trifluralin

3). GRLs are designed to emphasise the importance of GAP for growing quality tobacco. All Asian, African countries, Brazil and China also follow these GRL levels in exporting tobacco.

(a) Carbendazim is the degradation product of Benomyl and Thiophanate-methyl.Incase the same sample contains residues of both Carbendazim and/or Benomyl/Thiophanate-methyl, the sum of the residues should not exceed2ppm.

(b) Deltamethrin is the degradation product of Tralomethrin. In case the same sample contains residues of both Deltamethrin and Tralomethrin, the sum of the two residues should not exceed 1 ppm.

(c) Dichlorvos is the degradation product of Naled and Trichlorfon. In case the same sample contains residues of both Dichlorvos and/ or Naled/ Trichlorfon, the sum of the residues should not exceed 0.1ppm.

(d) Omethoate is the degradation product of Dimethoate. In case the same sample contains residues of both Dimethoate and Omethoate, the sum of the two residues should not exceed 0.5 ppm.

(e) The Dithiocarbamates Group includes the EBDCs: Mancozeb, Maneb, Metiram, Nabam and Zineb – as well as Amobam, Ferbam, Policarbamate, Propineb,Thiramand Ziram.

(f) Methomyl is the degradation product of Thiodicarb. In case the same sample contains residues of both Methomyl and Thiodicarb, the sum of the two residues should not exceed 1 ppm.

(g) Fluopyram added to GRL list June 2018.

(h) New CPA with GRL (November 2019).

(i) Flupyradifurone added to GRL list October 2020.

2.2 Unnoticed issue regarding organochlorine pesticide

Among DDTs, the parental compound had the highest concentration in Morocco cigarettes,followed by cigarettes from Indonesia. These levels along with a pp'DDT/ pp'DDE ratio above indicate a recent use of DDT in these two countries or where the tobacco used for producing these cigarettes was cultivated. In Indonesia the amount of tobacco produced is on average 200,000metric tons per year; in Morocco it is just 2,000 metric tons so, in this case, tobacco leaves are likely imported from the surrounding African countries (WHO, 2018). These results agree with arecent review executed by Bogdal et al., 2013 which reported higher levels of DDTs in ambient air in somecountries of Africa and the Pacific Islands, reflecting the DDT use for malaria control in these regions. pp'DDE had the highest value in Italian cigars made of Kentucky tobacco locally produced. In Italy, DDT use was banned in 1978 but Dicofol (an acaricide containing DDT) production continued until 1996 and secondary sources of contamination are currently present (Bettinetti et al., 2008). Cigars from Cuba had high levels of both pp'DDT and pp'DDE, and the pp'DDT/ pp'DDE ratio lower than 1 suggests a possible reduction in recent years of the use of this pesticide than in the past. Relatively high DDTs levels were also found in Mexican and Indian cigarettes. The tobacco used to produce Mexican cigarettes is probably cultivated in the southern part of the country where DDT is used in an endemic malaria region and a pp'DDT/pp'DDE ratio above 1 was found in soil samples (Wong et al., 2010). Also works reporting pp'DDT/ pp'DDE ratio in Indian soil and air samples (Pozo et al., 2011; Mishra et al., 2012; Yadav et al., 2015) suggested some ongoing use of DDT in agricultural areas of India. Such as for the two Chinesebrands, Zheng et al. (2010) found a variable ratio between pp'DDE and its parental compound in air on an urban–rural transect across Tianjin; higher pp'DDT concentrations were found in areas where DDTs are locally produced or in the proximity to a harbor probably due to the large number of fishing ships on which DDT-containing antifouling paints are used regularly.

In Indian scenario, the status of organochlorine pesticide residues in Indian FC tobacco tells that in Mysore district of Karnataka and West Godavari district of Andhra Pradesh the detection levels of DDT were 1.7–3.3 times lower than that of the GRL of total DDT (0.2 mg kg^{-1}). DDT is a phased out chemical for agricultural use in India, with a limited and legally restricted application for public health purposes. The reason for detection of DDT in those limited samples could

be because of the transfer of persisting residues of DDT from environmental components (Mukherjee and Gopal 2002; Bakore et al. 2004; Rahman et al. 2012, Ghosh et al., 2014). Traces of total endosulfan residues (ranging from 0.08– 0.16 mg kg^{-1}) were detected very few in Mysore district Karnataka and Prakasam district, Nellore district and West Godavari district of Andhra Pradesh. These residues were 6.25–12.5 times lower than that of the GRL of total endosulfan (1.00 mg kg^{-1}). Lindane was detected only in three samples (detection range 0.02–0.03 mg kg^{-1}) from Prakasam district of Andhra Pradesh which were 1.67– 2.5 times below the CORESTA issued GRL (0.05 mg kg^{-1}). The total HCH was detected only in one sample from East Godavari district of Andhra Pradesh. The important point to note that none of the samples from East Godavari were found to have lindane, but one sample had total HCH which is a combination of HCH isomers (á-HCH, â-HCH and ä HCH). This indicated that though there was no application of lindane (ã-HCH), but the encountered residues of total HCH might be a resulting from the transfer of persisting HCH residues from environmental components to the plant in Indian condition also (Kumari et al. 2004; Prakash et al. 2004). The tobacco samples collected from the Hassan district of Karnataka and Krishna district of Andhra Pradesh were also devoid of all ten organochlorine pesticide residues.

3. Current status of pesticide usage in tobacco

Previous research mentions the presence of certain active ingredients (AIs) in cigarette and smoke (Asubiojo et al. 2009; Dane et al. 2006; Jebet et al. 2018; Qamar et al. 2019; WHO 2015). Mainly, organochlorine pesticides are found in the study of Asubiojo et al. (2009) and Guthrie (1968). Permethrin and captan are cited in samples taken in 2009 and 2011 by Jebet et al. (2018). Nitropesticides have been reported in the work of Dane et al. (2006). As new AIs have been developed in recent years to treat tobacco, it is now questioned whether they alsocan be found in the tobacco smoke. In Cuba, no research was conducted on this topic in recent years.

In 2013, the yearly per capita consumption of the Cuban population of 15 years and older (9,310,462inhabitants) was 1405 cigarettes (3.8 cigarettes perday) (Lugo 2014). In 2016, the annual percapita consumption increased to 1657 cigarettes (4.5cigarettes per day) (Lugo 2017). In 2017,very similar figures were reported: 1612 cigarettes(4.5 cigarettes per day) were smoked per year (Suárez-Lugo 2018). The current Cuban context is not very encouraging. Abreu-Gutiérrez and Suárez-Lugo (2018) report in a recent study that the starting age for tobacco consumption is as early as 13.5 years, whereas other studies state that 74.8% starts before they are 20 years old (Suárez-Lugo 2018). Most youngsters are influenced mainly by friends (46.9%), and start smoking as a fashion or just out of curiosity (42.9%).The prices of tobacco products in Cuba make them accessible for all (Suárez-Lugo and Galceran-Serrat 2018). A high proportion of the Cuban population (83.7%) is aware of tobacco addiction; almost all ofthem (91.8%) know the consequences of smoking; and many of them (75.5%) have a perception of therisk of smoking. In 69.4% of non-smokers' homes, there are also smokers present. Among the American countries, Cuba ranks fifth in the prevalence of smoking, with 23.7% of the population over 15 years of age smoking (Varona Pérez et al. 2016). In Cuba, smoking is also reported as a serious health problem. Eight out of ten deaths are related to cigarettes, and 86% of them die from lung cancer (Varona Pérez et al. 2015; Varona Pérez et al. 2016). The most recent data on mortality associated with tobacco consumption in Cuba show that in 2013, 13,303 Cubans died as a result of smoking. This high mortality together with the high prevalence turns smoking into a chronic problem (Ávila et al. 2016). The different kind of pesticides used in tobacco and their usage are enlisted in Table 3 and 4.

Most of these pesticides were also widely used on food crops. The actual number and amount of pesticides used on tobacco or other crops in any given year vary depending on factors such as the weather and the specific pests that become problematic. For example, the incidence of many plant diseases are closely correlated to the amount of rainfall, resulting in greater use of fungicides in years with high rainfall. In addition, pesticide use tends to change over time as pests develop resistance to the pesticides and as use on tobacco is approved for new pesticides and cancelled for

Table 4: Pesticides Commonly Used on Tobacco

Types	Pesticides
Insecticide	Acephate, aldicarb, Bacillus thuringiensis, carbaryl,carbofuran, chlorpyrifos, diazinon, disulfoton,endosulfan, ethoprop, fenamiphos, fonofos,imidacloprid, malathion, methidathion, methomyl,spinosad, trichlorfon
Herbicide	Benefin, clomazone, diphenamid, isopropalin, napropamide, pebulate, pendimethalin, sethoxydim, sulfentrazone
Fungicide	Dimethomorph, mancozeb, mefenoxam, metalaxyl
Plant growth regulator	Ethephon, flumetralin
Plant growth regulator, herbicide	Maleic hydrazide
Fumigant, insecticide	Chloropicrin
Fumigant, insecticide, herbicide	Methyl bromide
Fungicide, insecticide, herbicide	1,3-dichloropropene (1,3-D)

Source: EPA, International Organization for Standardization, National Center for Food and Agricultural Policy, and USDA.

Table 4: Pesticide use on Tobacco

Pesticide	Kg used on tobacco (19th Century survey)	Kg used on tobacco (20th Century survey)
1,3-dichloropropene (1,3-D)	5,233,347	5,975,678
Chloropicrin	261,760	3,042,740
Maleic hydrazide	811,572	805,540
Acephate	712,348	392,355
Methyl bromide	2,429,783	308,262
Pendimethalin	146,026	213,173
Chlorpyrifos	310,962	183,070
Fenamiphos	116,638	170,928
Mancozeb	2,576	160,565
Metalaxyl	168,576	122,116
Ethoprop	198,798	82,044
Pebulate	186,880	59,249
Ethephon	51,364	45,959
Napropamide	87,017	42,013
Sulfentrazone	39,909	31,331
Imidacloprid	3,787,320	30,797
Aldicarb	72,141	27,088
Dimethomorph	252,102	16,700
Methomyl	25,917	13,505
Malathion	3,424	7,002
Disulfoton	23,849	6,121
Spinosad	26,244	4,345
Carbaryl	60,953	1,277
Fonofos	207,045	933
Benefin	25,838	766
Bacillus thuringiensis	4,475	39,637
Carbofuran	68,023	28,886
Diazinon	24,344	30,560
Diphenamid	37,024	34,669
Isopropalin	58,644	1,517
Methidathion	31	1,558
Trichlorfon	327	3,888

Source: National Center for Food and Agricultural Policy.

older pesticides (Cozzani et al., 2020). As table 2 shows, 10 pesticides identified in the 19th Century survey as commonly used on tobacco were not identified in the earlier survey. Two of these pesticides, dimethomorph and mancozeb, began to be used in response to the appearance of a disease resistant to metalaxyl, which declined in usage during the 1990s. In addition, during the years included in the survey, tobacco use for 5 of the 7 pesticides no longer reported as being used—diazinon, diphenamid, isopropalin, methidathion, and trichlorfon—was being cancelled (Dieng et al., 2013). In some cases, pesticide cancellations resulted in the increased use of other pesticides. For example, by 1997clomazone had replaced diphenamid and isopropalin as the pesticide of choice for controlling unwanted weeds, and imidacloprid was most commonly used to control insect pests, leading to reduced use of acephate, aldicarb, chlorpyrifos, ethoprop, and carbofuran. Manufacturers may initiate cancellation of some or all uses of a pesticide, often for economic reasons (Dieng et al., 2014) or EPA may cancel uses when the agency determines that one or more uses pose unreasonable risks to human health or the environment. For example, as required under the Clean Air Act, EPA has been phasing out the use of methyl bromide on tobacco and a wide range of other crops because it depletes the earth's protective layer of ozone (Habanosaccesed on 10th July 2023)Methyl bromide use on tobacco decreased from about 5.4 million pounds in 1992 to about 0.7 million pounds in 1997 because of regulatory board's efforts and changes in how tobacco producers raise seedlings in different European countries. Specifically, producers have begun to grow tobacco seedlings in greenhouses, where methylbromide is not generally used. The pendimethalin residue in Indian condition are in below GRL in different district of Andhra Pradesh and Karnataka (0.0052-0.0169 mg kg^{-1}).

The regulatory authority determines the amounts and conditions under which a pesticide maybe used so that it will not pose unreasonable risks to workers or the general population. Failure to comply with the conditions set by EPA could result in a range of harmful effects. For example, 17 of the 37pesticides commonly used on tobacco in the 1990s belong to three chemical classes that, at high doses, are known to cause adverse human health effects up to and including death. Although they do not all produce their toxic effects in the same way, pesticides in these three classes—organochlorines, organophosphates, and carbamates—act on the nervous system to prevent the normal flow of nerve impulses to muscles that control both voluntary movement, such as walking, and involuntary movement, such as breathing and heart beat. Pesticides in all three classes are absorbed to varying degrees through inhalation, ingestion, and skin contact. Exposure to amounts of these pesticides that exceed levels set by EPA could result in immediate and life threatening effects, such as respiratory failure, or conditions that do not appear immediately, such as cancer. While EPA has concluded that most of these 17 pesticides do not cause birth defects, the agency has also concluded that 5 of them and a by-product of another may cause cancer (JMPR 1979).

Since the 1970s, regulatory authorities throughout the countries like USA, Europe, southern and Northern America has severely restricted its approvals of organo chlorine pesticides, which include DDT, aldrin, and chlordane, because of their potential to harm humans and the environment. Organochlorine pesticides persist in the environment—some have remained in soil for over 50 years—and accumulate in body tissue, particularly fat. Organochlorine pesticides are associated with a range of adverse health effects, including cancer and damage to the neurologicaland reproductive systems. The one organochlorine pesticide still approvedfor use on tobacco, endosulfan, is highly toxic when ingested or inhaledand slightly toxic through contact with the skin. While EPA hasdetermined that it is unlikely to cause cancer as other members of thisclass do, endosulfan, like all organochlorine pesticides, primarily affectsthe nervous system. EPA has requested additional data from themanufacturer to address its concerns that exposure to endosulfan couldharm the nervous system of developing fetuses. Organophosphate and carbamate pesticides have largely replaced the organochlorine pesticides in the United States. While they break down quickly in the environment and do not accumulatein body tissues, organophosphate pesticides are much more acutely toxicto humans and animals than the persistent organochlorine pesticides theyhave largely

replaced. The primary cause of death from organophosphatepoisoning is respiratory failure, although cardiovascular symptoms, suchas decreased heart rate that progresses to cardiac arrest, usually occur as well. In humans, additional symptoms from exposure to organophosphate pesticides, which can develop during use or within minutes to hours after exposure, include headache, nausea, dizziness, sweating, muscle twitching, anxiety, and depression. Exposure by inhalation causes the most rapid appearance of toxic symptoms. As a result, to minimize the potential for harmful exposure of workers, EPA requires those who mix,use, or apply the pesticides to have special training, use respirators, andwear chemical-resistant clothing. Regarding the potential to cause cancer, EPA has determined that 4 of the 10 organophosphate pesticides used on tobacco—acephate, ethoprop, methidathion, and trichlorfon—may cause cancer. In addition, EPA has concluded that 7 of the 8 organophosphate pesticides it evaluated for their potential to cause birth defects would not cause them but that the eighth—chlorpyrifos—may do so at very high levels that may also harm the pregnant female (Koszowski et al., 2009).

Carbamates, which also affect the central nervous system, produce symptoms similar to those of organophosphate pesticides, although the effects of carbamate poisoning tend to be of shorter duration and somewhat easier to treat. The primary cause of death from carbamate poisoning is respiratory failure. Of the six carbamate pesticides used on tobacco, EPA has determined that one and a by-product always associatedwith another may cause cancer; two are unlikely to cause cancer; data areinsufficient to determine the cancer-causing potential of one; and one willbe evaluated in fiscal year 2003. EPA has evaluated four of the carbamates for their potential to cause birth defects: three do not and only minimal evidence exists for the potential of the fourth to cause birth defects. EPAhas requested, but not yet received, data from the manufacturer on the potential of one of the two remaining carbamate pesticides to produce birth defects, and the agency will evaluate the health effects of the other in fiscal year 2003.

Under its pesticide registration program, EPA routinely assesses the health risks of exposure to pesticides from residues in drinking water and food and from pesticide use in the home, in public places, and at work. The Health Effects Division of the Office of Pesticide Programs in EPA develops its health risk assessments on the basis of a substantial body of data, including toxicity, residue chemistry, and other data provided by pesticide manufacturers, as well as other relevant information, such as human and animal studies from the general scientific literature and poisoning incident databases. The risk assessments focus on the potential cancer and non cancer health risks associated with short-term (acute), intermediate-, and long-term (chronic) exposures to pesticides from the primary exposure routes—oral, inhalation, and contact with skin (dermal). Non cancer health risks that EPA assesses include risk of birth defects, reproductive impairments, damage to genetic material, and interference.

To evaluate the levels of pesticides to which cigarette smokers might be exposed from residues on tobacco, EPA reviews plant metabolism and residue studies provided by manufacturers that identify the residues ofpesticides, and any harmful by-products16 they may produce, that remainon the crop after it has been treated. The plant metabolism studies revealhow plants process a pesticide once it is applied and the relative amounts of the pesticide and its by-products that remain after treatment—the total toxic residue (TTR). The residue studies, called field trials, quantify the levels of pesticide and by-product residues that remain on plants grown under actual agricultural conditions that approximate the expected "reallife" environment. Such field trial data, which are required for all pesticides that will be used on food, may not always be required for pesticides used on tobacco because EPA uses a "tiered" approach to evaluate residues on tobacco. That is, for tobacco, the agency requires additional residue data after the metabolism study only if it has shown that the combined residue levels of the pesticide itself and any harmful by-products exceed 0.1 parts per million (ppm)—the agency's "threshold of concern" for residues on tobacco. Thus, as figure 1 shows, EPA generally requires plant metabolism studies for green tobacco and may require data from field trials for both green and cured (aged) tobacco, depending upon the amount of residues that are identified (Krebs et al., 2016) In addition,EPA may

require pyrolysis studies that measure the residues in smoke when tobacco treated with a pesticide is burned. Finally, EPA may require additional residue studies to estimate potential exposure, even if the residues are below 0.1 ppm, if it has concerns about the toxicity of a pesticide.

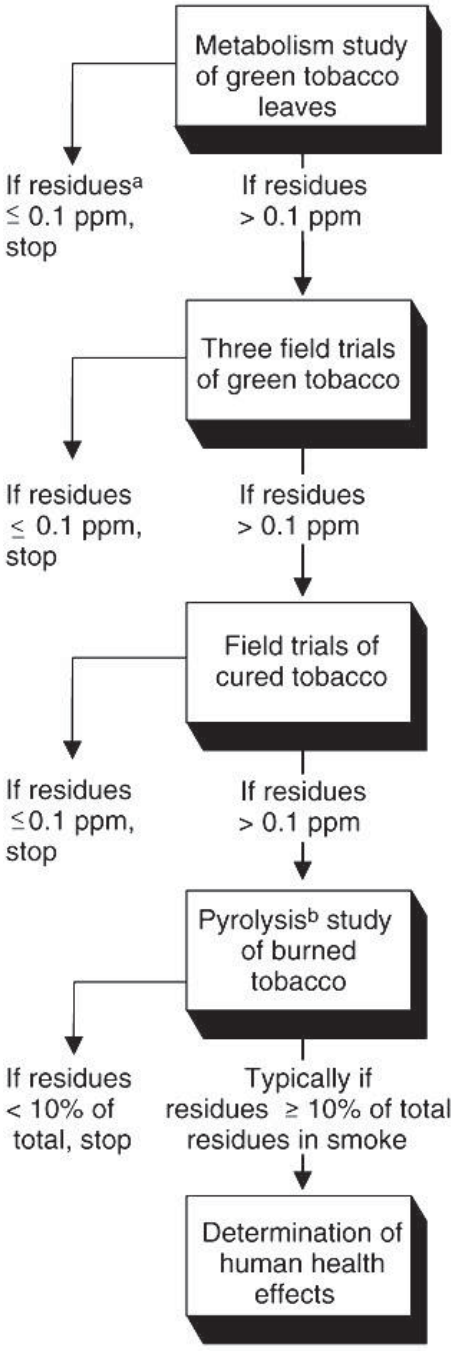

Fig: 1 Tiered Approach to Assessing Health Risks of Exposure to Residues on Tobacco

The tiered approach to analyzing residues on tobacco reflects the fact that, typically, pesticide residues on tobacco decline over time, as the tobacco is stored, cured, manufactured into cigarettes, and burned during smoking (Rahman et al., 0212).

4. Identification and quantification techniques used for pesticide residue analysis

Very few reports are available which elaborates the identification and quantification techniques of pesticide residues in tobacco. New methods to analyse pesticide residues in tobacco samples have been described in recent years (Bernardi et al. 2016; Khan et al. 2014, 2015; Yan-bo et al. 2015). Paul et al. (2021) established ORBITRAP based untargeted analysis of pesticides using HRMS based technologies, which has been very efficient with screening detection limit of 40 ppb. The high resolution accurate mass analysis was performed through sequential full-scan (resolution = 350 0 0) and variable data independent acquisition (resolution = 17500) events. When the method was evaluated in a mixture of 181 pesticides, it effectively minimised matrix interferences and false negatives. The target compounds included 5 pairs of isomers and 27 pairs of isobars, which were distinguished based on chromatographic separation, mass resolving power and/or unique product ions. The screening detection limit (SDL) for 86.4% of the test pes- ticides was set at 5 ng/g, while the remainder had the SDLs at 10 ng/g (9.3%) and 40 ng/g (4.3%). Nearly, 75% of the compounds showed recoveries of 75–120% at 10 ng/g. The rest of the compounds showed satisfactory recoveries at 40 and 100 ng/g. In all cases, precision-RSDs were < 20%. The established method demonstrated a successful performance in four different types of tobacco matrices while aligning with the guidelines of SANTE and US-FDA (Table 5). Owing to its efficiency, the method is recommended for screening and quantitation of multiclass pesticides in tobacco. The LOQ level was 40 ng/g for 18 compounds which included aldicarb, cyazofamid, cyproconazole, diflubenzuron, ethiofencarb, ethion, flonicamid, fluopicolide, halosulfuron- methyl, iodosulfuron-methyl, methiocarb, methomyl, oxamyl, pendimethalin, propanil, pyrithiobac, spirodiclofen and thioben- carb. At this level, 163 compounds

(89% of the total number) exhibited average recoveries from 70 to 120%. For the remaining eight compounds, namely boscalid, chlorsulfuron, fenoxycarb, parathion-methyl-oxon, phorate-sulfone, phosalone, propargite and tolclofos-methyl, the LOQs were between 40 and 100 ng/g. Consid- ering the variation in LOQs and the requirements of multiresidue validation, the recovery of the aforementioned compounds was checked at the harmonised fortification level of 100 ng/g (below their GRLs). In another study Bie et al. (2022) analyses and quantifies the Multiclass Pesticide Residues in Tobacco by Gas Chromatography Quadrupole Time-of-Flight Mass Spectrometry Combined with Mini Solid-Phase Extraction. Under the optimized conditions, 92% of the pesticides showed satisfactory recoveries of 70%–120% with precision <20% at spiking levels of 50,250, and 500 ng/g. The limits of detection and quantification for all the analyses were 0.05–29.9 ng/gand 0.20–98.8 ng/g, respectively. In addition, a screening method based on the retention time and a homebuilt high-resolution mass spectrometry database were established. Under the proposed screening parameters and at spiking levels of 50, 100, and 500 ng/g, 76.6%, 94.7%, and 99.0% multiclass pesticide residues were detected, respectively, using the workflow software. The validated method was successfully applied to the analysis of real tobacco samples. Thus, the combination of mini-SPE and GC-QTOF/MS serves as a suitable method for the quantitative analysis and rapid screening of multiclass pesticide residues in tobacco.

5. Novel methodology used for new generation pesticide residue analysis

ORBITRAP based untargeted analysis of pesticides using HRMS based technologies, which has been very efficient with screening detection limit of 40 ppb (Paul et al., 2021). Although more research need to be carried out to explore about the novel methodology to be used for new generation pesticide residue analysis in tobacco.

6. A way forward towards the exporting of quality tobacco with acceptable GRL

To ensure that pesticides can be used without posing an unreasonable risk to human health, different regulatory bodies viz., EPA, USDA, CORESTA conduct risk assessments of exposures to the pesticides it evaluates for use in the different countries worldwide, including exposure to pesticide residues on tobacco. Their decision to limit its quantitative assessment of the risks associated with pesticides on tobacco to the effects of short-term exposure, and not include the long-term exposure of smokers, recognizes that the pesticides are used on a crop that itself poses very significant health risks to humans through use in various consumer products—primarily cigarettes. Overall, health risk assessments show that the pesticides used on tobacco and other crops are probably a greater hazard for those who handle them than for those who inhale tobacco smoke. Nonetheless, while the risks of some exposures,

Table 5: Quantification and identification techniques useful for pesticide residue analysis on tobacco

Quantification/Identification technique	Recoveries	Reference
ORBITRAP-HRMS,	75-120%	Paul et al., 2021
GC-QTOF/MS	70-120%	Bie et al., 2022
UPLC-MS/MS	80-120%	Bernardi et al. 2016
GC-MS-MS	70-120%	Khan et al. 2014, 2015
GC-MS	70-120%	Yan-bo et al. 2015
HPLC-PDA	60-100%	Rahman et al., 2012
LC-MS-MS	65-100%	Yang et al., 2014

such as acute poisoning, are clear, less is known with certainty about the effects of long-term exposure to small amounts of pesticides, such as residues in food and water, on tobacco, or in the environment.

While historically the quality control unit of all regulatory bodies has required pesticide manufacturers to provide data on the residues remaining on tobacco, its assessments of the health effects associated with exposure to the residues were not identified in risk assessment documents and generally were not quantified. Mirroring the improvements in risk assessment methods in recent years, it has been adopted a more formal and consistent approach to evaluating the health risks associated with pesticides used on tobacco and has started to document, in its risk assessment documents, its conclusions on the potential for short-term risks from pesticide residues that may remain in tobacco smoke. As a result, interested parties are better informed about the potential risks, and the regulatory bodies are appropriately more accountable for its assessments to export quality tobacco.

7. CONCLUSION

Protection of the public interest hinges on an open process and regulatory agencies' willingness to stand up to pressure from regulated industries. When these are in doubt, public confidence in the fairness and efficacy of regulations may be unwarranted. The resource disparities between powerful industries and public health organizations may also make it difficult to ensure that the public interest is fairly represented, particularly when discussions occur behind closed doors, as apparently occurred at the U.S. EPA. Increased public and media scrutiny of these processes could help ensure that public health considerations are weighed at least as heavily as commercial ones. Finally, given the deadly epidemic of tobacco-caused disease, which kills an estimated5 million people annually worldwide(WHO 2004), is it in the public interest for regulatory agencies today to continue facilitating standards that make it easier and less costly to grow, transport, store, and manufacture tobacco products?

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