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SIGNIFICANCE OF IMPURITIES IN THE SAFETY EVALUATION OF CROP PROTECTION PRODUCTS

(IUPAC Technical Report)

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Significance of impurities in the safety evaluation of crop protection products

(IUPAC Technical Report)

Abstract: There may be substantial differences in the chemical composition of technical-grade products of the same active ingredient manufactured under different conditions, from different raw materials, or by different routes of synthesis. Resulting differences in impurity content may significantly affect the toxicological properties of pesticide products. Relevant impurities are those that may exhibit pronounced toxic effects compared to the active ingredient, affect phytotoxicity or physical properties of formulations, result in undesirable residues in food, or cause environmental contamination. The first safety assessment of an active ingredient by a regulatory body considers toxicological data developed on a representative batch of technical products, with the assumption that the material produced commercially by the original or generic manufacturers has an equal or higher content of active ingredient and contains the same or fewer impurities at equal or lower concentrations as the fully characterized technical product used in the toxicological tests. Three steps are essential for ensuring the safety of commercial technical-grade pesticide products, whether produced by the original manufacturer or by generic manufacturers. First, the identity and chemical structure of the impurities must be elucidated. This should include positive identification of major (≥1 %) and all toxicologically or environmentally relevant impurities, and characterization of minor impurities (≥0.1 %). Second, in addition to recognition of a minimum active ingredient content, official specifications should also list relevant impurities and their maximum permissible concentrations. Implementation of these specifications should be aided by a decision-making scheme for establishing similarity of subsequently evaluated technical products. Third, appropriate analytical methods for the detection and quantification of impurity levels should be developed and employed in a quality-monitoring program associated with the manufacturing and formulation process.

RECOMMENDATIONS OF THE IUPAC COMMISSION ON AGROCHEMICALS AND THE ENVIRONMENT

1. Detailed information on the composition of the technical active ingredient of the pesticide to be registered and toxicological studies applicable to the particular product should always be made available to regulatory agencies.
2. Relevant impurities should be defined as those that are more toxic than the pure active ingredient or raise other toxicological concerns, cause phytotoxicity, taint food commodities, affect the physical properties of formulations, or result in significant residues in food or the environment.
3. The relevant impurities should be named and their maximum permissible concentration should be specified in the registration documents as well as in Food and Agriculture Organization (FAO) Specifications of Plant Protection Products. Other impurities may be considered confidential.
4. The toxicological evaluations of the FAO/WHO (World Health Organization) Joint Meeting on Pesticide Residues, based on a specified technical-grade material, are carried out to assess the safety of food containing pesticide residues. These evaluations are not designed to cover aspects

of occupational health. Therefore, they should not be used alone to grant registration for a pesticide.

5. The registration authorities should evaluate the pesticide products made by different manufacturers individually. Registration for a pesticide product should not be granted without specification of its manufacturer(s) and manufacturing site(s). The approved suppliers of active ingredients used for formulation of pesticides should also be specified.
6. The comprehensive safety and efficacy evaluation for registration of a pesticide is not solely sufficient to assure safe use of the product. In order to avoid undesirable effects, the pesticides must be properly stored and applied according to the approved label.
7. Public confidence in the quality of pesticides requires analysis and testing in a government monitoring and surveillance program. Therefore, the quality of pesticide products marketed and the concentration of their relevant impurities should also be checked as part of the regulatory control of the use of pesticides using laboratories equipped with appropriate instrumentation and expertise. Strict enforcement actions should be taken by national regulatory authorities for adherence to the approved specification.
8. Appropriate pesticide management systems and good storage practices should be implemented to avoid the creation of stocks of deteriorated pesticides. Authorization should only be given for the use of expired pesticides, with application rates increased to compensate for the lower active ingredient content, if toxic impurities are not present in the product at toxicologically significant concentrations, physical properties are acceptable and adverse effects such as phytotoxicity will not occur.
9. Independent laboratories may play an important role in improving safety of the use of pesticides by undertaking research on their composition and identifying potentially toxic impurities.
10. Manufacturers of pesticides should regularly check the chemical composition of technical-grade products to assure that their composition complies with quality specifications. The quality of technical-grade product used or purchased for preparing the commercial pesticide should be determined prior to formulation if reliable analytical records are not supplied by the manufacturer of the technical material.
11. Laboratories performing regulatory compliance testing of pesticides should have access to the technical material of typical composition, the gas chromatography (GC), high-pressure liquid chromatography (HPLC) chromatograms, and relevant spectra infrared (IR), mass spectrometry (MS), nuclear magnetic resonance (NMR), and ultraviolet and visible (UV–vis) of both the technical material and the formulated products with assignations for impurities. This information can be used to screen the quality of pesticides on the market and identify those that might contain impurities at higher amounts than specified or products deriving from other manufacturer(s) even if the laboratory is not equipped for the confirmation and quantitative determination of impurities.
12. As the composition of products may be substantially different depending on the manufacturing process and materials used, the Collaborative International Pesticide Analytical Council (CIPAC) methods should be validated for each particular product before use if the pesticide is produced by more than one manufacturer. The FAO specifications should provide in an annex to the specifications the typical spectra and chromatograms of the technical-grade active ingredients for reference.
13. An impurity should be described in specifications by its systematic name and Chemical Abstract Services (CAS) registry number. In addition, for convenience, the impurity may be described by a brief name such as a common name, a generally accepted acronym or a derivative of a common name.

1. INTRODUCTION

Humans can be exposed to pesticides and their impurities through direct handling, re-entry of treated areas, contact with environmental residues, and dietary intake. Occupational and accidental exposure to these compounds should be evaluated primarily on the basis of acute toxicity and mutagenicity, whereas in the case of dietary intake, the chronic toxicity should also be taken into account.

Technical pesticides, although by definition being "pure active ingredient", also may contain complex mixtures of other minor chemical components due to process variables, side reactions, and impurities in starting materials. The impurities may contribute to the toxicity of the pesticide or may alter the physical properties of the product. For some impurities, this may lead to the allocation of maximum concentration limits in technical-grade products.

The toxicological tests carried out with technical products of typical composition for registration purposes include assessment of toxic potency of the impurities present in the test material. However, the composition of the technical product may vary, particularly with respect to impurities and potentially also the toxicity of the product, depending on the manufacturing process and sources of starting materials. The use of various adjuvants and carrier materials in the preparation of the formulation may also result in marked differences in storage stability of formulations. This is especially of concern in the case of generic pesticides, which may be produced and formulated by many manufacturers under widely varying conditions, with different materials, and under a range of quality control standards.

Because the composition of technical products can reveal the manufacturing process, information on the composition of technical active ingredients and formulations of pesticides is considered to be commercially confidential. It is usually available only for government registration authorities and relevant international advisory committees on a confidential basis. Consequently, this paper is based on the information published in the open literature. Because of such limitations, the report cannot provide comprehensive coverage of the extremely diverse subject. Rather, published examples are given to illustrate possible scenarios and support the conclusions and recommendations made.

This report is aimed at improving the safety assessment of crop protection products by focusing on the nature and effects of certain impurities. The topic of cross-contamination with other active ingredients, which may occur in a formulation plant, is not included in this review. Recommendations are provided to government authorities considering the establishment or revision of their pesticide registration and compliance programs to ensure the safe and efficient use of pesticides. Guidance is also given for the correct assessment of impurities in technical-grade and formulated pesticide products based on the technical documentation provided by the manufacturer, appropriate utilization of FAO Specifications of Plant Protection Products [1], and the toxicological evaluations made by the FAO/WHO Joint Meeting on Pesticide Residues [2]. The importance of regular control of relevant impurities during the manufacturing and formulating processes as well as during storage and handling of marketed products is highlighted.

2. REPORTED IMPURITIES IN PESTICIDES

Many impurities of various chemical classes may be present in a technical pesticide product; they may be carried over from the starting materials or formed during synthesis or storage and handling. For example, Fig. 1 illustrates impurities reported in technical malathion.

The impurities identified or likely to be present in some pesticides, and their concentration ranges found in commercial samples, are summarized in Table 1. This table also includes the pesticides for which the permissible maximum concentration of impurities are included in the FAO Specifications for Plant Protection Products published up to 2000 [1]. The new procedure for development and use of FAO Specifications for Plant Protection Products [3] requires information on the impurities in the technical products, and the new FAO specifications will include all relevant impurities.

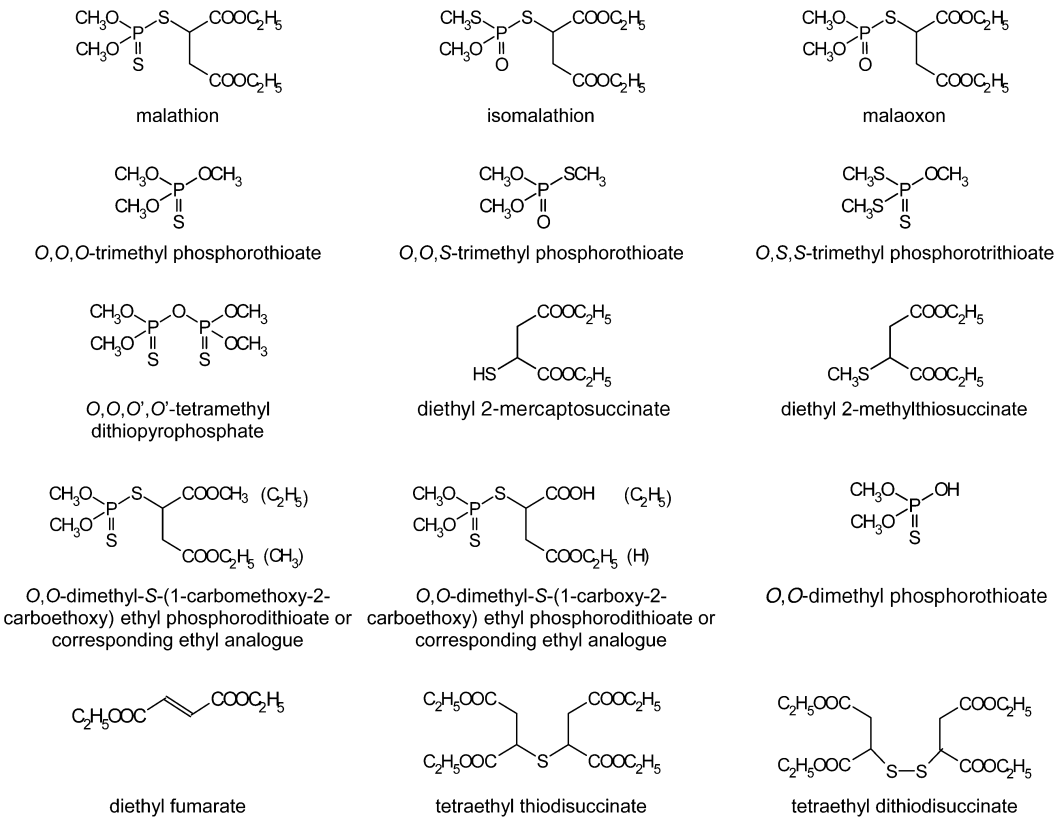


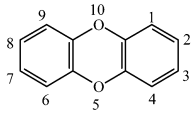
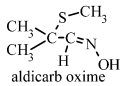
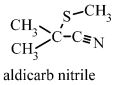
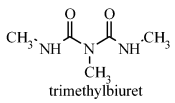
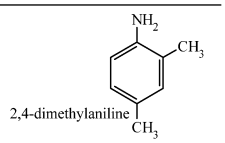
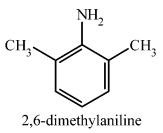
Fig. 1 Malathion and impurities in technical malathion.

Because of their relatively high toxicity, special attention will be given to several groups of compounds including chlorinated dibenzodioxins, halogenated dibenzofurans, chlorinated azobenzenes, nitrosamines, ethylenethiourea, biphenyl ethers, anilines and substituted anilines, hydrazines, phenols, and iso-thiophosphorus esters as well as oxon, sulfoxide, and sulfone derivatives of organophosphorus and carbamate compounds. The occurrence and toxic effects of some of these compounds will be discussed in Section 3, which deals with relevance of impurities.

2.1 Effects of storage on impurity formation

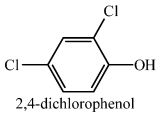
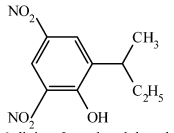
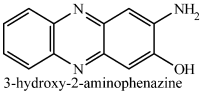
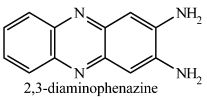
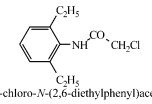
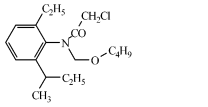
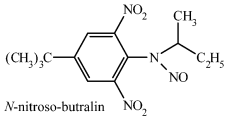
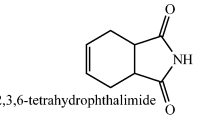
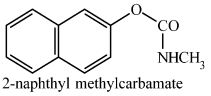
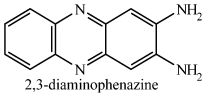
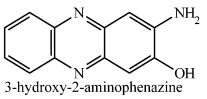
Chlorpyrifos formulations of varying ages were analyzed for 3,5,6-trichloro-2-pyridinol (TCP) and sulfotep. Levels of TCP ranged between <0.05–0.12 %, 0.1–0.2 %, 0.19–3.8 %, and 0.4–0.57 % in samples stored for 1, 3, 4, and 5 years, respectively. The sulfotep content of the commercial products did not show any correlation with storage time. One 2-year-old sample containing 13.8 % TCP, 0.65 % sulfotep and trace amounts of chlorpyrifos oxon was reported as the cause of the death of 50 bulls treated directly with the product for ecto-parasite control [4]. Though the TCP was unlikely related to the toxicity of the product, the higher-than-normal levels detected were an indication of lengthy storage under adverse conditions.

Table 1 Impurities reported or likely to be present[a] in pesticides.

Active ingredient Chemical name/formula of impurities	Specified max. conc.[b]	Reported conc.[c]	References[d]	
2,4,5-T				
2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD)	0.01 mg/kg	0.1–55 mg/kg	[7]	
free phenols max.	5 g/kg[e]			
2,4-D				
2,7-dichlorodioxins				
1,3,7-trichlorodioxins		12–23 µg/kg[g]	[8]	
1,3,6,8/1,3,7,9-tetrachlorodioxins		2–5 µg/kg[h]		
2,3,7,8-tetrachlorodioxin	0.01 mg/kg		[9]	dioxins
free phenols	3 g/kg[f]		[1]	
free phenols	5 g/kg[f]		[1]	
2,4-DB Dichlorprop				
free phenols	15 g/kg[f]		[1]	
Acephate				
$(CH_3O)_2P(O)NH_2$	5 g/kg		[1]	
$(CH_3O)_2P(S)NHC(O)CH_3$	1 g/kg		[10]	
$(CH_3O)_2P(O)SCH_3$				
acetamide	1 g/kg			
Alachlor				
2-chloro-2,6-diethylacetanilide	30 g/kg		[1]	
Aldicarb				
aldicarb oxime	4.0 g/kg		[1]	
$(CH_3)_2C(OC_2H_5)CH{=}NOCONHCH_3$			[6]	aldicarb oxime
$(CH_3)_2C(SOCH_3)CH{=}NOCONHCH_3$				
aldicarb nitrile	53.0 g/kg			
$CH_3NHCONHCH_3$				aldicarb nitrile
$CH_3NHCON(CONHCH_3)CH_3$				
$(CH_3)_2C(SCH_3)CH{=}NOCON(CONHCH_3)CH_3$				
methyl isocyanate	12.5 g/kg			
trimethylamine	12.5 g/kg			trimethylbiuret
dimethylurea + trimethylbiuret	50 g/kg			
Alpha-cypermethrin				
triethylamine	1 g/kg		[11]	
Aluminum phosphide				
arsenic	0.04 g/kg		[1,12]	
Amitraz				
2,4-dimethylaniline	3 g/kg		[13]	
				2,4-dimethylaniline
Benalaxyl				
2,6-dimethylaniline	1 g/kg		[14]	
				2,6-dimethylaniline

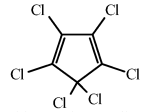
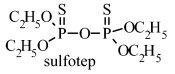
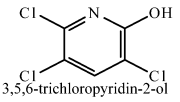
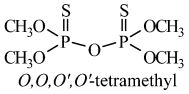
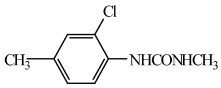
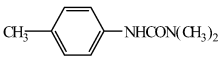
(*continues on next page*)

Table 1 (*Continued*).

Active ingredient Chemical name/formula of impurities	Specified max. conc.[b]	Reported conc.[c]	References[d]	
Bifenox				
2,4-dichlorophenol	3 g/kg		[1]	 2,4-dichlorophenol
2,4-dichloroanisole	6 g/kg			
Binapacryl				
4,6-dinitro-2-*sec*-butylphenol			[15]	 4,6-dinitro-2-*sec*-butylphenol
Benomyl				
3-hydroxy-2-aminophenazine	0.5 mg/kg		[1]	 3-hydroxy-2-aminophenazine
2,3-diaminophenazine	0.5 mg/kg		[16]	 2,3-diaminophenazine
Butachlor				
2-chloro-*N*-(2,6-diethylphenyl)acetamide	0.2 g/kg		[1]	 2-chloro-*N*-(2,6-diethylphenyl)acetamide)
dibutoxymethane	13 g/kg			
butyl chloroacetate	10 g/kg			
2-chloro-*N*-[2-ethyl-6-(1-methylpropyl) phenyl]-*N*-(butoxymethyl)acetamide	14 g/kg			 2-chloro-*N*-[2-ethyl-6-(1-methylpropyl)phenyl] -*N*-butoxymethyl)acetamide
Butralin				
N-nitroso-butralin	1 mg/kg		[13,16]	 *N*-nitroso-butralin
N-nitroso-dimethylpropylamine	0.5 mg/kg			
Captan				
1,2,3,6-tetrahydrophthalimide			[6]	 1,2,3,6-tetrahydrophthalimide
THPhiSO_2CCl_3				
perchloromethylmercaptan (CCl_3SH)				
Carbaryl				
2-naphthol	0.05 %		[1]	 2-naphthyl methylcarbamate
2-naphthyl methylcarbamate	0.05 %			
Carbendazim				
2,3 diaminophenazine	3 mg/kg		[1]	 2,3-diaminophenazine
3-hydroxy-2-aminophenazine	0.5 mg/kg			 3-hydroxy-2-aminophenazine
Carbosulfan				
carbofuran	20 g/kg		[1]	

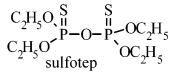
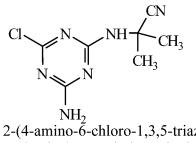
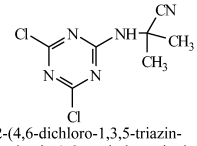
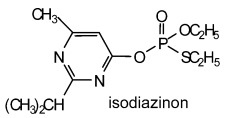
(*continues on next page*)

Table 1 (*Continued*).

Active ingredient Chemical name/formula of impurities	Specified max. conc.[b]	Reported conc.[c]	References[d]	
Chlorbenside				
disulfides	1.0 %[i]		[1]	
Chlordane				
hexachlorocyclopentadiene	1.0 %		[1]	 hexachlorocyclopentadiene
Chloridazone				
4-amino-5-chloro-isomer	60 g/kg		[1]	
Chlorothalonil				
hexachlorobenzene	0.1*, 0.3 g/kg		[13[a],1]	
Chlorpropham				
chloroaniline	250 µg/kg		[1]	
Chlorpyrifos				
sulfotep[b,c]		0.01 %*	b: [17]	 sulfotep
		0.15–065 %*	c: [4]	
3,5,6-trichloropyridinol		<0.05–0.57 %*	[6]	 3,5,6-trichloropyridin-2-ol
$(C_2H_5O)_2P(S)PYCl_2$ (Cl are in 3,6 or 5,6 positions)				
$(C_2H_5O)_2P(S)PYCl_3$ (Cl are in 3,4,6; 4,5,6 positions)				
$(C_2H_5O)_2P(S)PYCl_4$				
$(C_2H_5O)(C_2H_5S)P(O)PYCl_3$				
Chlorpyrifos-methyl				
O,*O*,*O*′,*O*′-tetramethyl dithiopyrophosphate			[16[j]]	 *O,O,O′,O′*-tetramethyl dithiopyrophosphate
Chlorthal-dimethyl				
2,3,7,8-tetrachlorodibenzo-*p*-dioxin	0.01 mg/kg		[18]	
hexachlorobenzene	100 mg/kg		[1]	
hexachlorodibenzo-p-dioxin	0.01 mg/kg			
Chlortoluron				
3-(3-chloro-4-tolyl)-1-methylurea	8 g/kg		[1]	 3-(3-chloro-4-tolyl)-1-methylurea
3-(4-tolyl)-1,1-dimethylurea	8 g/kg			 3-(4-tolyl)-1,1-dimethylurea
Copper oxychloride				
arsenic	50 mg/kg		[1]	
lead	250 mg/kg	137–1037 mg/kg	[19]	
cadmium	50 mg/kg	22.5–351 mg/kg		

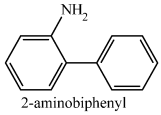
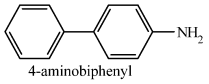
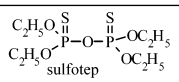
(*continues on next page*)

Table 1 (*Continued*).

Active ingredient Chemical name/formula of impurities	Specified max. conc.[b]	Reported conc.[c]	References[d]	
Coumaphos				
sulfotep	0.04–0.06 %		[17]	 sulfotep
Cyanazine				
2-(4-amino-6-chloro-1,3,5-triazin-2-ylamino)-2-methyl propionitrile	20 g/kg		[1]	 2-(4-amino-6-chloro-1,3,5-triazin-2-ylamino)-2-methyl propionitrile
2-(4,6-dichloro-1,3,5-triazin-2-ylamino)-2-methyl propionitrile	3 g/kg			
simazine	10 g/kg			 2-(4,6-dichloro-1,3,5-triazin-2-ylamino)-2-methyl propionitrile
Daminozide				
1,1-dimethylhydrazine	50 mg/kg		[16]	
N-nitrosodimethylamine	2 mg/kg			
Deltamethrin				
deltamethrin R isomer	10 g/kg		[11]	
Demeton				See: chloryrifos
sulfotep		3.1–3.6 %*	[17a]	
Diazinon				
sulfotep*	2.5 g/kg	0.3–0.4 %*	[11]	 isodiazinon
		<0.01–0.53 %*	a: [20]	
			b: [17]	
$(C_2H_5O)(C_2H_5S)_2PS$			[6]	
$(C_2H_5O)_2(C_2H_5S)PS$				
$(C_2H_5O)_3PS$				
$(C_2H_5O)(C_2H_5S)_2PO$				
isodiazinon				
PyrH				
$PyrP(S)(SC_2H_5)(OC_2H_5)$				
$(C_2H_5O)P(S)NHC(NH)CH(CH_3)_2$				
Dicamba				Note: positions of substituents were not specified in original publication.
$C_6H_3Cl_2OH$			[6]	
$Cl_2C_6H_2(OH)COOH$				
$Cl_2C_6H_2(OCH_3)COOCH_3$				
$ClC_6H_3(OCH_3)COOH$				
$Cl_3C_6H(OCH_3)COOH$				
Dichlorphen				
4-chlorophenol	20 g/kg		[21]	
Dichlorvos				
chloral	5 g/kg		[1,12]	

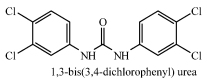
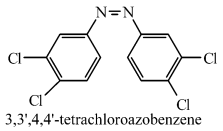
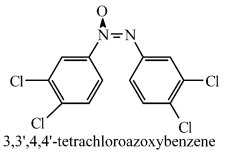
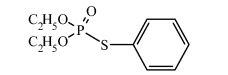
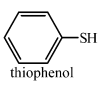
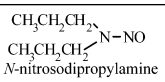
(*continues on next page*)

Table 1 (*Continued*).

Active ingredient Chemical name/formula of impurities	Specified max. conc.[b]	Reported conc.[c]	References[d]	
Dicofol			[1]	
o,o′-DDE, *o,m′*-DDE, *o,p′*-DDE, *m,p′*-DDE, *p,p′*-DDE, *o,p′*-chloro-DDT, *p,p′*-chloro-DDT	1 g/kg	≤575* g/kg dicofol[k]	a: [22]	
Dimethoate				
$(CH_3O)_2P(S)SH$			[6]	
$(CH_3O)_2(CH_3S)PS$				
$(CH_3O)_3PS$				
$(CH_3O)_2P(S)SSP(S)(OCH_3)_2$				
$ClCH_2CONHCH_3$				
$(CH_3O)_2P(S)SCH_2CON(CH_3)_2$				
$(CH_3O)_2P(S)SCH_2COOH$				
$(CH_3O)CH_3S)P(O)SCH_2CONHCH_3$				
O,O,O′,O′-tetramethyl dithiopyrophosphate	5 g/kg		[11,9[j]]	
$(CH_3O)_2P(O)SCH_2CONHCH_3$ (omethoate)	5 g/kg		[1,9]	
Dimefox				
schradan	12 %		[1]	
hexamethylphophoramide	12 %			
Dinobuton				
free dinoseb and its salts	5 g/kg		[1]	
Dinocap				
2-(1-methylheptyl)-4,6-dinitrophenyl methyl ether			[23]	
2-(1-ethylhexyl)-4,6-dinitrophenyl methyl ether				
2-(1-*n*-propylpentyl)-4,6-dinitrophenyl methyl ether				
4-(1-methylheptyl)-2,6-dinitrophenyl methyl ether				
4-(1-ethylhexyl)-2,6-dinitrophenyl methyl ether				
4-(1-*n*-propylpentyl)-2,6-dinitrophenyl methyl ether				
Dinoseb				
$C_4H_9C_6H_3(NO_2)OH$			[6]	Note: positions of substituents not specified in original publication.
$(C_4H_9)_2C_6H_2(NO_2)OH$				
$C_4H_9C_6H_2(NO_2)_2OC_4H_9$				
$C_6H_4(NO_2)_2OH$				
$C_4H_9C_6H_2(SO_3H)(NO_2)OH$				
Diphenylamine				
aniline	5 mg/kg		[13,16]	 2-aminobiphenyl
2-aminobiphenyl	20 mg/kg			
4-aminobiphenyl	1 mg/kg			 4-aminobiphenyl
Diquat				
free 2,2′-bipyridyl	10 mg/kg		[1]	
ethylene dibromide	10 mg/kg			
Disulfoton				
sulfotep	2 g/kg	0.01 %*	[24] a: [17]	 sulfotep

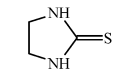
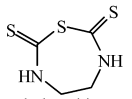
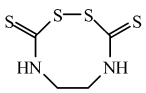
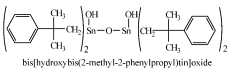
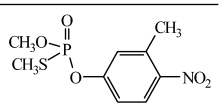
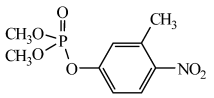
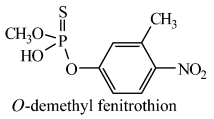
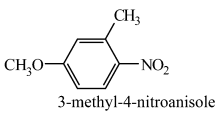
(*continues on next page*)

Table 1 (*Continued*).

Active ingredient Chemical name/formula of impurities	Specified max. conc.[b]	Reported conc.[c]	References[d]	
Diuron				 1,3-bis(3,4-dichlorophenyl) urea
1,3-bis(3,4-dichlorophenyl)urea			[25,26]	
3,3′,4,4′-tetrachloroazoxybenzene	1*, 2* mg/kg		a: [1]	
3,3′,4,4′-tetrachloroazobenzene (TCAB)	10*, 20* mg/kg		b: [24]	
free amine salts	0.4 %*,l			 3,3',4,4'-tetrachloroazobenzene
				 3,3',4,4'-tetrachloroazoxybenzene
DSMA				
antimony	2.2 g/kg		[13]	
pentavalent inorganic arsenic	27 g/kg			
trivalent inorganic arsenic	2.2 g/kg			
Edifenphos				 *O,O*-diethyl-*S*-phenyl phosphorothioate
O,*O*-diethyl *S*-phenyl phosphorothioate	2 g/kg		[1]	
Thiophenol	2 g/kg			 thiophenol
Endosulfan				
endosulfan-ether	10 g/kg		[1]	
endosulfan-alcohol	20 g/kg			
EPTC				 *N*-nitrosodipropylamine
N-nitrosodipropylamine (NDPA)		0.09–0.36 mg/kg	[27]	
Ethephon				
$(HO)_2P(O)CH_2CH_2P(O)(OH)_2$			[28]	
$ClCH_2CH_2P(O)(OH)CH_2CH_2Cl$				
$ClCH_2CH_2OCH_2CH_2P(O)(OH)_2$				
$H_2C{=}CHP(O)(OH)_2$				
$HOCH_2CH_2P(O)(OH)_2$				
$HP(O)(OH)_2$				
$HOP(O)(OH)_2$				
Ethion				See: chlorpyrifos
sulfotep	2 g/kg		[24]	

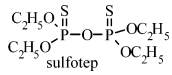
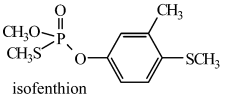
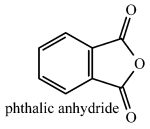
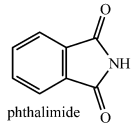
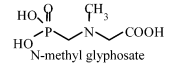
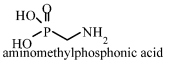
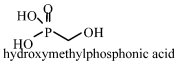
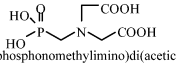
(*continues on next page*)

Table 1 (*Continued*).

Active ingredient Chemical name/formula of impurities	Specified max. conc.[b]	Reported conc.[c]	References[d]	
Ethylenebisdithiocarbamates			[29]	
ethylenethiourea	0.5 %	0.02–2.0 %[*]	b: [30]	 ethylenethiourea
ethylenethiuram monosulfide		0.04–2.0 %[*, m]	c: [31]	 ethylenethiuram monosulfide
ethylenethiuram disulfide				 ethylenethiuram disulfide
Ethoxyethyl-mercury chloride				
other organomercurials max:	10 %[n]		[1]	
Ethoxyethyl-mercury silicate				
other organomercurials	10 %[o]		[1]	
Fenbutatin oxide				
bis[hydroxybis(2-methyl-2-phenylpropyl)tin] oxide	20 g/kg		[1]	 bis[hydroxybis(2-methyl-2-phenylpropyl)tin]oxide
Fenitrothion				
S-methyl fenitrothion	20 g/kg[*]		a: [11]	 *S*-methyl fenitrothion
fenitrothion-oxon			[31,32]	
O-methyl-*O*,*O*-bis(3-methyl-4-nitrophenyl) phosphorothioate				
O-methyl-*O*,*O*-(3-methyl-4-nitrophenyl) phosphate	2 %[p]		[1]	 fenitrothion oxon
$(CH_3O)_3PS$				
3-methyl-4-nitrophenol				
S-methyl-*O*,*O*-bis(3-methyl-4-nitrophenyl) phosphorothioate			[33]	
$(CH_3O)_2(CH_3S)P(S)$			[34]	 *O*-demethyl fenitrothion
$(CH_3O)_2P(S)Cl$				
$(CH_3O)_2P(S)O\ P(S)\ (CH_3O)_2$				
O-methyl-*O*-(3-methyl-4-nitrophenyl) phosphorothioate (demethyl fenitrothion)			[8]	 3-methyl-4-nitroanisole
S-methyl-*O*-(3-methyl-4-nitrophenyl) phosphorothioate				
3-methyl-6-nitrophenol				
3-methyl-4-nitroanisole				
Fenoprop				
free phenols	15 g/kg[f]		[1]	
2,3,7,8-tetrachlorodibenzo-*p*-dioxin	0.01 µg/g			
Fenoprop potassium salt				
free phenols[e]	15 g/kg		[1]	
2,3,7,8-tetrachlorodibenzo-*p*-dioxin	0.01 µg/g			

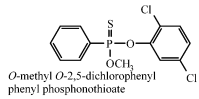
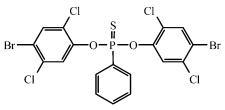
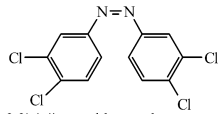
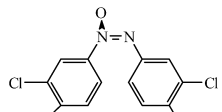
(*continues on next page*)

Table 1 (*Continued*).

Active ingredient Chemical name/formula of impurities	Specified max. conc.[b]	Reported conc.[c]	References[d]	
Fensulfothion				
sulfotep		0.01 %*	b: [17]	 sulfotep
$(C_2H_5O)_2(C_2H_5S)PS$			[6]	
$(C_2H_5O)_3PS$				
$(C_2H_5O)_2P(S)SSP(S)(OC_2H_5)_2$				
$(C_2H_5O)_2P(S)Cl$				
$4\text{-}HOC_6H_4SCH_3$				
$(C_2H_5O)_2P(S)OC_6H_4\text{-}p\text{-}SCH_3$				
$(C_2H_5O)_2P(S)OC_6H_4\text{-}o\text{-}SCH_3$				
$4\text{-}HOC_6H_4SOCH_3$				
$(C_2H_5O)_2P(S)OC_6H_4\text{-}p\text{-}SO_2CH_3$				
$(C_2H_5O)_2P(S)OC_6H_5$				
$(C_2H_5O)_2(C_2H_5S)P(O)O\ C_6H_5$				
Fenthion			[35]	
isofenthion			[9][j]	 isofenthion
O,*O*,*O*′,*O*′-tetramethyl dithiopyrophosphate				
Folpet				
phthalic anhydride			[6]	 phthalic anhydride
phthalimide				 phthalimide
$PhiSO_2CCl_3$				
Furalaxyl				
2,6-dimethylaniline	500 mg/kg		[13,21]	
Glyphosate acid				
N-methylglyphosate	28 g/kg		[1]	 N-methyl glyphosate
aminomethylphosphonic acid	17 g/kg			
hydroxymethylphosphonic acid	12 g/kg			 aminomethylphosphonic acid
(phosphonomethylimino)di(acetic acid)	10 g/kg			 hydroxymethylphosphonic acid
N-nitrosoglyphosate	1 mg/kg			 (phosphonomethylimino)di(acetic acid)
Heptachlor				
hexachlorocyclopentadiene	1.0 %		[1]	
Hexazinone				
carbamic acid ethyl ester	50 mg/kg		[1]	
Isoproturon				
ortho isomer	10 g/kg		[1]	
meta isomer	20 g/kg			
Lambda-cyhalothrin				
triethylamine	1 g/kg		[11]	

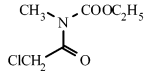
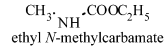
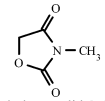
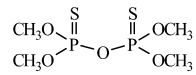
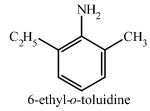
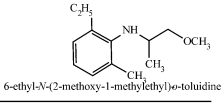
(*continues on next page*)

Table 1 (*Continued*).

Active ingredient Chemical name/formula of impurities	Specified max. conc.[b]	Reported conc.[c]	References[d]	
Leptophos				
O,*O*-dimethyl phenyl phosphorothioate			[36]	 *O*-methyl *O*-2,5-dichlorophenyl phenyl phosphonothioate
O-methyl *O*-2,5-dichlorophenyl phenyl phosphonothioate				
O,*O*-bis(4-bromo-2,5-dichlorophenyl) phenyl phosphonothioate				 *O*,*O*-bis(4-bromo-2,5-dichlorophenyl) phenyl phosphonothioate
Lindane				
alpha –HCH	5 % of γ isomer		[11]	
Linuron				
3,3′,4,4′-tetrachloroazobenzene (TCAB)	20 mg/kg[*,q]		A: [24,26]	 3,3',4,4'-tetrachloroazobenzene
3,3′,4,4′-tetrachloroazoxybenzene	2 mg/kg			 3,3',4,4'-tetrachloroazoxybenzene
free amine salts	0.4 %[r]			
Malathion				
$(CH_3O)_3P{=}S$			[6,37–39]	
$(CH_3O)_2P(S)SCH_3$				
$(CH_3O)_2P(O)OCH_3$				
$(CH_3O)_2P(S)OP(S)(OCH_3)_2$				
$(CH_3O)_2P(S)SP(S)(OCH_3)_2$				
malaoxon	1 g/kg			
$(CH_3O)_2P(S)SH$			[13]	
isomalathion	2 g/kg			
$(CH_3S)_2P(O)OCH_3$	1.8 %[s]		[13]	
$(CH_3O)(CH_3S)P(S)SC(CH_2COOCH_3)CHOOC_2H_5$			[11]	
$(CH_3O)(CH_3S)P(S)SC(CH_2COOC_2H_5)CHOOCH_3$				
$(CH_3O)(CH_3S)P(S)SC(CH_2COOC_2H_5)CHOOH$				
$(CH_3O)(CH_3S)P(S)SC(CH_2COOH)CHOOC_2H_5$				
$HSC(CH_2COOC_2H_5)CHOOC_2H_5$				
$S[C(CH_2COOC_2H_5)CHOOC_2H_5]_2$				
$(CH_2COOC_2H_5)C_2H_5OOCHSSC(CH_2COOC_2H_5)CHOOC_2H_5$				
Mancozeb				
ETU	0.5 %		[1]	
Maneb				
ETU	0.5 %		[1]	
Maleic hydrazide				
hydrazine	15 mg/kg[t]		[13]	
MCPA				
free phenols	10 g/kg[u]		[1]	
triethanolamine insolubles				

(*continues on next page*)

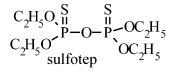
Table 1 (*Continued*).

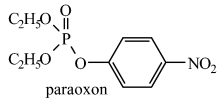
Active ingredient Chemical name/formula of impurities	Specified max. conc.[b]	Reported conc.[c]	References[d]	
MCPB				
free phenols	30 g/kg[u]		[1]	
Mecarbam				
ethyl *N*-methyl-*N*-chloroacetyl carbamate	2 %		[1]	 ethyl *N*-methyl-*N*-chloroacetylcarbamate
ethyl *N*-methyl carbamate	2 %			 ethyl *N*-methylcarbamate
3-methyl-oxazolid-2,4-dione	1 %			 3-methyl-oxazolid-2,4-dione
O,*O*,*S*-triethyl phosphorothiolothionate	1.2 %			
O,*O*,*O*-triethyl phosphorothionate	1.0 %			
Mecoprop				
free phenols	15 g/kg[u]		[1]	
Metalaxyl				
2,6-dimethylaniline	1 g/kg		[1,9]	
Methacrifos				
O,*O*,*O*′,*O*′-tetramethyl dithiopyrophosphate				
O,*O*,*O*-trimethyl phosphorothioate	70 g/kg		[1,13][j]	 *O*,*O*,*O*′,*O*′-tetramethyl dithiopyrophosphate
O,*O*-dimethyl phosphoramidothioate	90 g/kg			
O,*O*,*S*-trimethyl phosphorothioate	1 g/kg			
Methamidophos				
O,*O*-dimethyl phosphoramidothioate	90 g/kg		[1]	
N-methylamidate	80 g/kg		[35]	
O,*O*,*S*-trimethyl phosphoramidothioate	20 g/kg			
$(CH_3O)_3P{=}S$	70 g/kg			
Methomyl				
$CH_3CONHOH$			[6]	
$CH_3C(SCH_3){=}NOH$				
$CH_3C(Cl){=}NOCONHCH_3$				
$CH_3CH{=}NOCONHCH_3$				
Methoxychlor				
chloral hydrate	2.5 g/kg		[1,11]	
Metolachlor				
6-ethyl-*o*-toluidine	1 g/kg		[1]	 6-ethyl-*o*-toluidine
6-ethyl-*N*-(2-methoxy-1-methylethyl)-*o*-toluidine	2 g/kg			 6-ethyl-*N*-(2-methoxy-1-methylethyl)-*o*-toluidine
2-chloro-6-ethylaceto-*o*-toluidine	15 g/kg			
Methoxyethyl-mercury chloride				
other organomercurials	10 %[v]		[1]	
Methoxyethylmercury silicate				
other organomercurials	10 %[w]		[1]	

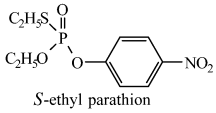
(*continues on next page*)

Table 1 (*Continued*).

Active ingredient Chemical name/formula of impurities	Specified max. conc.[b]	Reported conc.[c]	References[d]
Monocrotophos			
$(CH_3O)P(O)H$		0.5 %	[40]
$(CH_3O)P(O)OH$		1 %	
$(CH_3O)_3P$		0.75 %	
$(CH_3O)_3P(O)$	20 g/kg	1.5 %	[1,13]
$(CH_3O)(OH)P(O)OC(CH_3)=CHCONHCH_3$			
$(CH_3O)_2P(O)OC(CH_3)=CHCONH_2$			
$(CH_3O)_2P(O)OC(CH_3)=CHCONHCH_2OH$			
7 other compounds containing no phosphorus atom			
Monuron			
p-$ClC_6H_4NH_2$			[6]
4-$ClC_6H_4NHCONHC_6H_4Cl$-4			
4-$ClC_6H_4NHCONHCH_3$			
4-$ClC_6H_4NHCON(CH_3)_2$			
free amine salts	0.4 %[x]	FAO	
MSMA			
antimony	2.2 g/kg		[13]
pentavalent inorganic arsenic	27 g/kg		
trivalent inorganic arsenic	2.2 g/kg		
Naptalam			
2-naphthylamine	0.15 mg/kg		[13]
Omethoate			
trimethyl phosphate	20 g/kg		[1,24]
Oryzalin			
N-nitroso-di-*n*-propylamine	0.5 mg/kg		[13]
Oxyfluorfen			
N-nitrosodimethylamine	2 mg/kg		[24]
Paraquat			
free 4,4′-bipyridyl	0.2 %		[1,13]
2,2′:6′,2-terpyridine	3 mg/kg		
Parathion			
sulfotep	2 g/kg		[9]
$(C_2H_5O)_2P(S)SC_2H_5$			[41,6]
$(C_2H_5O)_3P(S)$			
$(C_2H_5O)P(S)S(C_2H_5)_2(C_2H_5O)_2P(S)SP(S)(C_2H_5)_2$			
$(C_2H_5O)_2P(S)SSP(S)(C_2H_5)_2$			
$(C_2H_5O)_2P(O)SC_2H_5$			
$(C_2H_5O)_2P(O)$			
$C_6H_4(NO_2)OH$			
$(C_2H_5O)(C_2H_5S)P(S)OC_6H_4NO_2$			
paraoxon			
S-ethyl parathion			
$(C_2H_5O)_2P(O)OH$			
free *p*-nitrophenol	1.0 %[y]		[1]

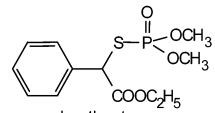
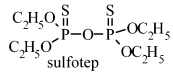

sulfotep


paraoxon


S-ethyl parathion

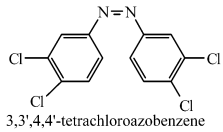
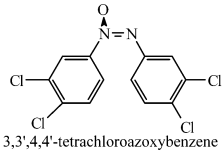
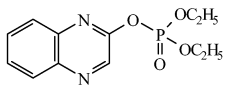
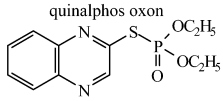
(*continues on next page*)

Table 1 (*Continued*).

Active ingredient Chemical name/formula of impurities	Specified max. conc.[b]	Reported conc.[c]	References[d]	
Parathion-methyl				
O,*O*,*O*′,*O*′-tetramethyl dithiopyrophosphate			[6]	
$(CH_3O)_2P(S)SCH_3$			[9][j]	
$(CH_3O)_3P(S)$				
$(CH_3O)P(S)(SCH_3)_2$				
$(CH_3O)_2P(S)SP(S)(CH_3)_2$				
$(CH_3O)_2P(S)SSP(S)(CH_3)_2$				
$(CH_3O)_2P(O)SCH_3$				
$(CH_3O)_2P(O)$				
$C_6H_4(NO_2)OH$				
$(CH_3O)(CH_3S)P(S)OC_6H_4NO_2$				
$(CH_3O)_2P(O)OC_6H_4NO_2$				
$(CH_3O)(CH_3S)P(O)OC_6H_4NO_2$				
$(CH_3O)_2P(O)OH$				
free *p*-nitrophenol	2 %[y]		[1]	
Pendimethalin				
N-nitroso-diethylpropylamine	0.5 mg/kg		[13]	
N-nitroso-pendimethalin	60 mg/kg			
Pentachlorophenol				
TCDD				
tetrachlorophenol			[42]	
hexa and octachlorodioxins			[43]	
Phenthoate				
isophenthoate			[38]	
$(CH_3O)_2P(S)SCH_3$				
$(CH_3S)_2P(O)OCH_3$				
phenthoate oxon	0.5 %		[1]	phenthoate oxon
Phenylmercury acetate				
other organomercurials max:	5.0 %[z]		[1]	
Phorate				
sulfotep	2 g/kg		[24]	
$(C_2H_5O)_2P(S)SC_2H_5$				sulfotep
$(C_2H_5O)_3P(S)$				
$(C_2H_5O)_2P(S)SCH_2OH$				
$(C_2H_5O)(C_2H_5S)P(S)SCH_2SC_2H_5$				
$(C_2H_5O)(C_2H_5S)P(S)SCH_2OC_2H_5$				
Phosalone				
sulfotep		0.01 %	[17]	See: phorate
Phoxim				
O,*O*,*O*,*O*-tetraethyl monothiodiphosphate			[35]	
Picloram				
hexachlorobenzene	100 mg/kg		[13,16]	
Pirimiphos-methyl				
O,*O*,*O*′,*O*′-tetramethyl dithiopyrophosphate			[12][j]	

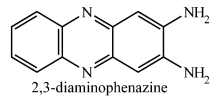
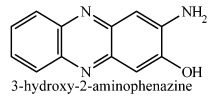
(*continues on next page*)

Table 1 (*Continued*).

Active ingredient Chemical name/formula of impurities	Specified max. conc.[b]	Reported conc.[c]	References[d]	
Prochloraz				
2,3,7,8-tetrachlorodibenzo-*p*-dioxin	0.01 mg/kg		[13]	
hexachlorobenzene	100 mg/kg			
hexachlorodibenzo-*p*-dioxin	4 mg/kg			
Prodiamine				
N-nitroso-di-*n*-propylamine	0.5 mg/kg		[13,24]	
Profenofos				
4-bromo-2-chlorophenol	1 %		[1]	
Propachlor				
N,N-diisopropylaniline	20 g/kg		[1]	
2-chloroacetanilide	18 g/kg			
2,2-dichloro-*N*-isopropylacetanilide		12 g/kg		
Propanil				
3,3′,4,4′-tetrachloroazobenzene (TCAB)	20 mg/kg	1.1–30 mg/kg*	[24]	 3,3',4,4'-tetrachloroazobenzene
tetrachloroazoxybenzene	2 mg/kg		[26]	 3,3',4,4'-tetrachloroazoxybenzene
Propham				
aniline	0.1 %		[1]	
Propoxur				
o-isopropoxyphenol	3.0 %		[1]	
Pyrazophos				See: chlorpyrifos
sulfotep	2 g/kg		[24]	
Pyrimethanil				
aniline	1 g/kg		[1,13]	
Quinalphos				
quinalphos oxon			[44]	 quinalphos oxon
isoquinalphos				
2-hydroxyquinoxalin				
quinoxalin-2-thiol				 isoquinalphos
diquinoxalin-2-yl sulfide				
diquinoxalin-2-yl disulfide				
dithienobisquinoxalin				
Quintozene				
hexachlorobenzene	75 mg/kg		[21,24]	

(*continues on next page*)

Table 1 (*Continued*).

Active ingredient Chemical name/formula of impurities	Specified max. conc.[b]	Reported conc.[c]	References[d]	
Simazine				
2,4-dichloro-N^6-ethyl-1,3,5-triazine-amine			[6]	
N^2, N^4, N^6-ethyl-1,3,5-triazine-triamine				
4-chloro-N^2,N^6-diethyl-1,3,5-triazine-diamine				
4-chloro-2-amino-N^6-ethyl-1,3,5-triazine-amine				
2-hydroxy -4-chloro-N^6-ethyl-1,3,5-triazine-amine				
2,4-dihydroxy- N^6-ethyl-1,3,5-triazine-amine				
4-hydroxy-N^2,N^6-diethyl-1,3,5-triazine-diamine				
Temephos				
O,*O*,*O*′,*O*′-tetramethyl dithiopyrophosphate			[24][j]	
Terbufos				
sulfotep		0.03 %	[17]	See: chlorpyrifos
Tetrachlorophenol				
hexa- and octachlorodioxines			[43]	
Tetradifon				
hexachlorobenzene	100 mg/kg		[18]	
Thiodicarb				
methomyl	5 g/kg		[1]	
Thiophanate methyl				
2,3-diaminophenazine	0.5 mg/kg[aa]		[1]	 2,3-diaminophenazine
3-hydroxy-2-aminophenazine	0.5 mg/kg			 3-hydroxy-2-aminophenazine
Thiofanox				
69 impurities			[45]	
Triadimefon				
4-chlorophenol	0.5 %		[1]	
Triadimenol				
4-chlorophenol	5 g/kg		[1,9]	
Trifluralin				
N-nitroso-di-*n*-propylamine	1 mg/kg	154 mg/l*	[1,12]	
$C_6H_2(NO_2)_2(CF_3)Cl$			b: [46]	
$C_6H_2(NO_2)(CF_3)Cl_2$			[6]	
$C_6H_2(NO_2)(CF_3)NPr_2$				
$C_6H_2(NO_2)_2(CF_3)OH$				
Zinc phosphide				
arsenic	0.04 g/kg		[1,21]	
Zineb				
ETU	0.5 %		[1]	
arsenic	200 mg/kg			
cadmium*		11.2–59 mg/kg*	a: [19]	

[a]The impurities were predicted by Baron and coworkers based on theoretical considerations. Since then, the presence of many of them was reported in technical products.

(*continues on next page*)

Table 1 (*Continued*).

[b]Maximum concentrations given in either by FAO, Australian (CAG), or Dutch national specifications. In pesticide specifications, the "concentration" is usually given as a mass fraction (e.g., g/kg), but other units may also be used. The units given in the original documents are quoted in the table.
[c]Impurities found in commercial samples.
[d]Authors reported the impurities in commercial pesticides are indicated with asterisks (*), while the authors described the impurities listed without any marks.
[e]Expressed as 2,4,5-trichlorophenol.
[f]Expressed as 2,4-dichlorophenol.
[g]Total dioxin content ranged from 11 to 16 300 µg/kg in 2,4-D esters. The main components were the di- and tri-chlorodioxins.
[h]Total dioxin content ranged from 1–3339 µg/kg in amine salt of 2,4-D, The main components were the di- and tri-chlorodioxins.
[i]Expressed as bis(4-chlorophenyl) disulfide.
[j]Limit is to be decided.
[k]Formulations manufactured before 1988 contained DDT related impurities at up to 575 g/kg of dicofol. Formulations manufactured after the EC Prohibition Directive, requiring that DDT-related impurities represent less than 1 g/kg dicofol content, contained these impurities at up to 7 g/kg of the dicofol.
[l]Calculated as dimethylamine HCl.
[m]ETU was present at higher concentrations, up to 2.73 %, in products stored for 5 years.
[n]Calculated as ethoxyethylmercury chloride.
[o]Calculated as ethoxyethylmercury silicate.
[p]Including other easily hydrolyzed impurities.
[q]10 m/kg and 1 mg/kg, respectively, in the Netherlands.
[r]Calculated as dimethylamine HCl.
[s]After stability test at 54 ºC for 6 days (note: the normal test is 14 days).
[t]1 mg/kg in the Netherlands.
[u]Expressed as 4-chloro-2-methylphenol.
[v]Calculated as methoxyethylmercury chloride.
[w]Calculated as methoxyethylmercury silicate.
[x]Calculated as dimethylamine HCl.
[y]Including *p*-nitrophenol from easily hydrolyzed impurities.
[z]Calculated as phenylmercury acetate.
[aa]Of the thiophanate-methyl content.

Under certain conditions, diazinon can deteriorate to harmful substances, particularly if the hydrocarbon solvent contains a small quantity of water (0.1–2 %). Exposure to air, light, and elevated temperature favor the formation of monothiotep (*O*,*S*-TEPP) and sulfotep (*S*,*S*-TEPP). These compounds are potent cholinesterase enzyme inhibitors and highly toxic. The cholinesterase inhibition activity of monothiotep was found to be about 14 000 times higher than that of diazinon. Levels of 1600 and 6600 mg/l, respectively, of sulfotep and monothiotep were found in date-expired samples of dog wash, sheep dip, and insect killer formulations. The water content of the samples ranged from 0.5 to 6.4 mg/ml [5].

S-methyl fenitrothion was found to be the major significant impurity in fenitrothion, especially in samples stored at ambient temperature for long periods of time [33]. The levels of fenitrothion oxon, as well as some other impurities, did not increase on storage indicating these compounds were by-products of the manufacturing process [8,47].

The results of investigations on impurities of malathion [31,48,49] during storage revealed that the formation of isomalathion was caused by the inert ingredients present in the formulation. A survey of 100 pesticide samples containing malathion in dust formulations, liquids, aerosols, and dry baits showed that over half were unstable on storage for one year. This was most likely due to the use of diluents and carriers, which catalyzed the decomposition of malathion. Postulated routes of formation of impurities during storage of malathion are shown in Fig. 2.

Technical quinalphos stored in open glass bottle at 30 °C for 6 months underwent degradation to give a black viscous mass containing the parent compound $(C_2H_5O)_2P(S)OQ$ (7.5 %), isoquinalphos $(C_2H_5O)_2P(O)SQ$ (5.8 %), quinalphos oxon $(C_2H_5O)_2P(O)OQ$ (3.2 %), 2-hydroxyquinoxalin QOH (12 %), quinoxalin-2-thiol QSH (18 %), diquinoxalin-2-yl-sulfide QSQ (15 %), diquinoxalin-2-yl-disulfide QSSQ (7 %), dithienobisquinoxalin $Q(S_2)Q$ (2.0 %), and at least 11 other compounds [44].

Unfavorable storage conditions may lead to the decomposition of pesticides to produce degradation products much more toxic than the active ingredient. The classic example is the nongenotoxic carcinogen ethylenethiourea (ETU), which is formed from the widely used ethylenebisdithiocarbamates (EBDCs) [29]. These EBDCs can be easily degraded in the presence of moisture, oxygen, and elevated temperature. The ETU is easily oxidized to ethyleneurea (EU).

A study on the stability of mancozeb formulations during storage under subtropical conditions indicated that ETU was the major degradation product. Ethylenethiuram monosulfide (ETM), ethylenethiuram disulfide (ETD), and 2-imidazoline were also detected in the samples. Mancozeb was found to be relatively more stable than zineb. Storage under closed conditions increased the stability of the compounds [29]. Lo and Ho [50] tested commercial formulations of EBDCs for ETU content, and found that nearly one-half (46.3 %) exceeded the specified level of 0.5 %. Zineb formulations were found to be the most frequently (77.9 % of samples) contaminated. Bontoyan and coworkers [31] tested the ETU content of 28 different EBDC formulations of 5 manufacturers. The samples of pesticides less than 2 years old contained ETU in the range of 0.04–2.02 %, whereas ETU was present at a level of 2.73 % in a product more than five years old.

Water and methanol content of formulations may result in hydrolysis of the active ingredient and formation of toxic impurities, as was shown in the case of malathion [39] and diazinon [5].

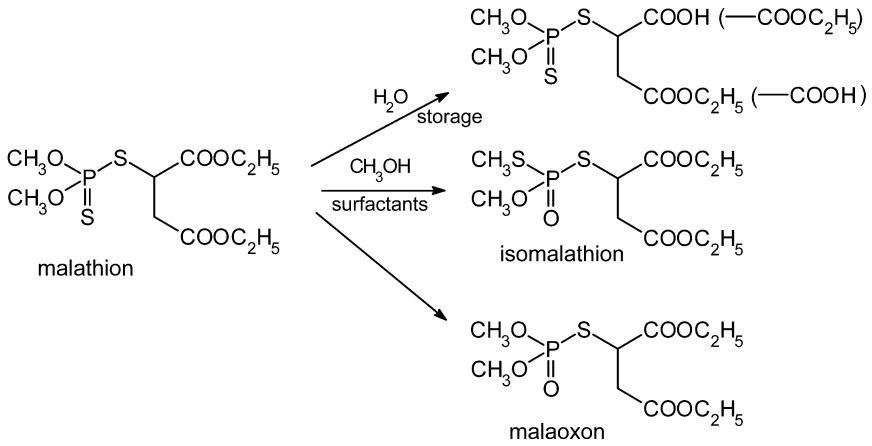


Fig. 2 Possible pathways for the formation of impurities of malathion during storage.

2.2 Analytical techniques for impurities

The identification of unknown impurities in a pesticide product at the mg/kg level is a very difficult analytical task because of the complex nature of technical products. Probably the best approach is to first

predict the possible impurities that may occur. This prediction may be aided by a study of the routes of synthesis in the manufacturing process, including identification of the main and side reactions, which may occur during synthesis as well as evaluation of possible impurities in the starting materials. In addition, consideration should be given to the known impurities in pesticides of similar chemical structure [6]. A survey of the literature may provide much useful information for the assessment. A second phase of effort is to look for the probable impurities in technical products by applying a combination of various chromatographic and spectroscopic methods.

Impurities of interest are usually analyzed by gas liquid chromatography (GLC), HPLC, and GC/MS (gas chromatography with mass spectrometric detection), alone or in combination with enrichment on chromatography columns [44,51] or initial separation on TLC plates [4]. Pavel and Kaiser [35] used TLC with enzyme inhibition or chemical detection to detect low concentrations of impurities in technical pesticides. Using this approach, detection limits of 1 μg and 0.03 ng, respectively, were reported for isofenthion and monothiotep (*O*,*O*,*O*,*O*-tetraethyl monothiodiphosphate), an impurity of phoxim. However, high-resolution GC/MS (up to 18 000) is required for the separation of dioxins from interfering compounds [43]. GC/MS alone cannot usually be used for identification of unknown substances [51]. In many cases, ^{1}H, ^{13}C, ^{31}P NMR [28,34,45], and other spectroscopic methods have been successfully applied for the identification of unknown impurities.

N-nitrosoamines can be detected with a thermal energy analyzer (TEA) and/or with GC/MS. TEA is much more selective and sensitive (about 100-fold more than TID and 1000-fold more than a UV detector) than the traditional nitrogen specific GC detectors and can be used at maximum sensitivity for the analysis of complex samples [49]. Capillary column GC/MS has a detection limit superior to that of the TEA. Comparisons carried out on a large number of samples showed good quantitative agreement [52].

3. RELEVANCE OF PESTICIDE IMPURITIES

The relevance of impurities is assessed by taking into account their relative toxicity compared with the active ingredient, their effect on the physical and chemical properties affecting the storage stability of the product, their phytotoxicity to treated crops, their production of taint in food crops or their resulting in undesirable residues in food or the environment. In addition to the impurities in the technical active ingredient, the composition and impurities of the carrier materials used in the formulations may also affect these properties of the product. Hence, they should also be taken into consideration for the safety assessment of the pesticides.

3.1 Toxicity of impurities

Even at their relatively low concentration in the pesticide product, impurities may in some cases be equally or substantially more toxic than the active ingredient. For instance, they may potentiate or synergize the toxicity of the active ingredient, cause delayed neurotoxicity, or have mutagenic or carcinogenic effects. The reported toxicity of a few example impurities is summarized in Table 2.

Table 2 Toxicity of some pesticides and their impurities.

Active ingredient		Impurities	
Name	LD_{50} mg/kg	Chemical name/formula	Toxicity (LD_{50} mg/kg)
2,4,5-T	500, rat	2,3,7,8-tetrachloro dibenzo-*p*-dioxin (TCDD)	630 000x, guinea pig 10 000x, rat
Benomyl		Phenazines	Mutagenicity
Carbendazim		Phenazines	Mutagenicity
Diazinon	300–400, rat 80–135, mice 250–355, guinea pig	Sulfotep	IC_{50} *O*,S-TEPP/diazinon = 14 000 (cholinesterase)
Fenitrothion		*S*-methyl isomer of fenitrothion	IC_{50} isofenitrothion/fenitrothion = 100–1000
Malathion	6100, mice 12 500, rat[b,c]	$(CH_3O)_3P{=}S$	1150, mice 15, rat
		$(CH_3O)_2P(S)SCH_3$	1850, mice[b] 15, rat[a,b]
		$(CH_3O)_2P(O)OCH_3$	400, mice
		$(CH_3O)_2P(S)OP(S)(OCH_3)_2$	25, mice
		$(CH_3O)_2P(S)SP(S)(OCH_3)_2$	1500, mice
		$(CH_3O)_2P(O)SC(CH_2COOC_2H_5)$-$CHOOC_2H_5$	215, mice
		$(CH_3O)_2P(S)SH$	1550, mice
		$(CH_3O)(CH_3S)P(O)SC$-$(CH_2COOC_2H_5)HCOOC_2H_5$	0.05 % in pure malathion: LD_{50}, rat: 4400 0.5 % in pure malathion LD_{50}, rat: 2000
		$(CH_3S)_2P(O)OCH_3$	26–43, rat 0.05 % in pure malathion: LD_{50}, rat: 3100 0.5 % in pure malathion: LD_{50}, rat: 1700

[a]Delayed toxicity.
[b]Ref. [10].
[c]Purified malathion.

3.1.1 Organophosphorus compounds

Combinations of some organophosphorus compounds and impurities present in the technical materials, arising either from synthesis or during storage, may lead to markedly different toxicities from what would be predicted from toxicities of the individual components.

Early investigations with technical parathion showed that it contained paraoxon and an *S*-ethyl isomer as impurities, which were responsible for the high anticholinesterase activity of the technical material. High-purity parathion, by contrast, is virtually devoid of anticholinesterase properties [53] as demonstrated by in vitro experiments. These contaminants, however, had very little effect on the in vivo toxicity of the parathion product to either insects or mammals.

In contrast to parathion, the acute mammalian toxicity of malathion and related organophosphorus insecticides, which contain a carboxylic ester, is strongly potentiated by impurities present in the technical material (Fig. 1).

Potentiation by impurities was first reported by Pellegrini and Santi [38], who demonstrated substantial increases in the rat toxicity of phenthoate and malathion when these materials were contaminated with small amounts of *O*,*S*,*S*-trimethyl phosphorotrithioate, *O*,*O*,*S*-trimethyl phosphorodithioate, and the respective *S*-methyl isomers of phenthoate (*S*-methyl phenthoate) and malathion (*S*-methyl malathion or isomalathion). Similar results for malathion and the phosphoroamidothioate insecticide

acephate were subsequently reported by Umetsu et al. [39], who examined the effects of impurities on acute rodent toxicity as determined by oral LD_{50} experiments.

Malathion, acephate and phenthoate contain acyl ester or amide moieties, which are vulnerable to hydrolytic degradation in biological systems (Fig. 3). The detoxification of malathion and phenthoate observed in mammals is related to the susceptibility of the carboethoxy moiety to hydrolytic degradation. The reaction, mediated by the carboxylesterases, evidently takes place in mammals at a rate faster than the activation reaction leading to formation of the potent anticholinesterase metabolites malaoxon or phenthoate oxon [54,55].

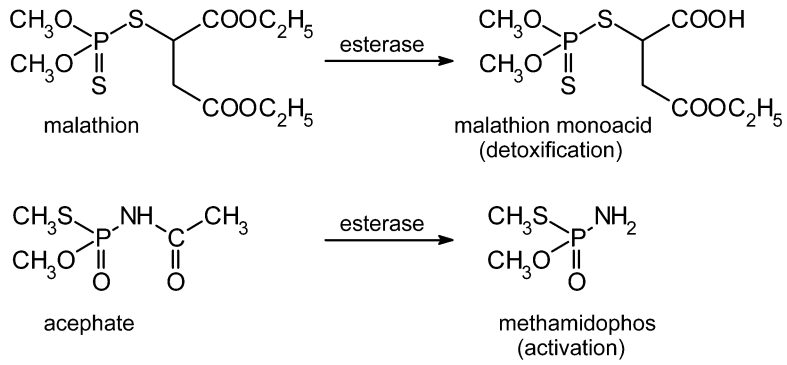


Fig. 3 Hydrolysis of malathion and acephate in biological systems.

On the other hand, the low mammalian toxicity of acephate is related to its inability to be activated to the corresponding phosphoramidothioate, the more active anticholinesterase compound methamidophos [56].

If the assumption is made that impurities in malathion and acephate interfere with esterase-catalyzed cleavage of the *O*-acyl or *N*-acyl linkages, respectively, then the impurities would be expected to have a potentiating effect on the toxicity of acephate. Potentiation studies indicated that the primary cause of potentiation appears to be carboxylesterase inhibition by the impurities. Linear correlation was observed between the serum and liver carboxylesterase activities and the malathion lethality in mice following treatment with selected impurities [37]. Although purified malathion had a rat oral LD_{50} of 12 500 mg/kg, contamination with as little as 0.05 % of the *S*-methyl isomer (isomalathion) or *O*,*S*,*S*-trimethyl phosphorodithioate resulted in LD_{50} values of 4400 and 3100 mg/kg, respectively. The toxicity of pure malathion containing 0.5 % of these two impurities was increased by factors of 6.3 and 7.2, respectively. The relative potency of malathion impurities for esterase inactivation has been shown to vary significantly, as summarized in Table 3 [10].

During the summer of 1976, thousands of cases of poisoning resulting from the use of malathion for malaria vector control were reported in Pakistan, resulting in at least five deaths [48]. Although these poisoning cases were primarily attributable to poor safety practices and hygiene, there is evidence that increased toxicity of poor-quality malathion also contributed to the poisonings. Toxicological evaluations revealed rat oral LD_{50} values as low as 325 mg/kg for one of the malathion brands used. In contrast, the rat oral LD_{50} of purified malathion has been reported to be as high as 12 500 mg/kg. The poor-quality malathion used in Pakistan had an *S*-methyl isomer content of 3.1 % as well as significant amounts of the *O*,*O*,*S*-trimethyl phosphorothioate and *O*,*S*,*S*-trimethyl phosphorodithioate impurities. Thus, the effect which impurities may have on the toxicity of malathion and related materials was made known to the public under very tragic circumstances.

Table 3 Inactivation of esterase by malathion impurities in vitro.

Compound	IC_{50} (mM)		
	Serum malathion carboxylesterase	Serum cholinesterase	Liver malathion carboxylesterase
$(CH_3O)_2P(S)SCH_3$	>5	>5	>5
Isomalathion	0.00045	0.003	0.0001
$(CH_3S)_2P(O)OCH_3$	0.04	0.17	0.002
$(CH_3O)_2P(O)SCH_3$	0.9	1.6	0.11

During the course of study of the potentiation of malathion by its impurities, it became evident that *O*,*O*,*S*-trimethyl phosphorothioate was highly toxic to rats by an unknown mode of action [57,58]. Compared with poisoning by an anticholinesterase organophosphorus insecticide, rats treated orally with *O*,*O*,*S*-trimethyl phosphorothioate remained alive longer. The LD_{50} value for this compound ranged from 15–60 mg/kg. Because of the extended period of time before death, the term "delayed toxicity" was used to describe intoxication induced by this compound. The delayed toxic activity of *O*,*O*,*S*-trimethyl phosphorodithioate, a strong potentiator of the acute toxicity of malathion and phenthoate to rats, was reported independently [60]. A number of analogs of *O*,*O*,*S*-trimethyl phosphorothioate [59], *O*,*O*,*S*-triethyl phosphorothioate (*O*,*O*,*S*-Et) and several other *O*,*O*,*S*-trialkyl phosphorothioates [54] and trialkyl phosphorodithioates [59] have also been found to exert delayed toxic activity. Typical signs of delayed toxic poisoning following a single oral dose of either 20–60 mg/kg *O*,*O*,*S*-trimethyl phosphorothioate or 20–40 mg/kg *O*,*O*,*S*-trimethyl phosphorodithioate were weight loss, red staining around the nose and mouth, and refusal of food or water. Animals which lost 40 % or more of their original weight invariably died four days to about three weeks following treatment. Death in many cases appeared to be attributable to respiratory failure. The lungs of rats treated with *O*,*O*,*S*-trimethyl phosphorodithioate revealed a number of abnormalities, including increases in wet and dry weight, enlargement, cellular proliferation with progressive diffuse interstitial thickening, and necrosis of type 1 alveolar cells [61–63]. *O,O*,*S*-trimethyl phosphorothioate caused a substantial increase in the amount of amino acids as well as a change in the nature of proteins excreted in the urine of treated rats [64,65]. Nearly identical results were obtained following treatment of rats with *O*,*O*,*S*-trimethyl phosphorodithioate [66]. Other poisoning signs following treatment with either *O*,*O*,*S*-trimethyl phosphorothioate or *O*,*O*,*S*-trimethyl phosphorodithioate included oliguria (decreased urine excretion), diuresis, and reduction in blood urea nitrogen/creatinine ratios. These changes in urine and blood parameters strongly suggest a mode of action for both compounds, which involves kidney tubule damage.

Immunosuppressive effects of an impurity of malathion, *O*,*O*,*S*-trimethyl phosphorothioate have been reported [67]. *O*,*O*,*S*-trimethyl phosphorothioate preincubated with GSH has an inhibitory effect on cytotoxic T lymphocytes and the hemolytic plaque-forming cell responses, mediated by a direct inhibitory effect on macrophages, T and B cells. Furthermore, interactions of *O*,*O*,*S*-trimethyl phosphorothioate and *O*,*O*,*S*-trimethyl phosphorodithioate with supercoiled DNA have been studied, and results indicate a possible covalent intercalation of these compounds as well as strand nicking of DNA [68].

Some other organophosphorus compounds, particularly phenylphosphonothioates, may also produce delayed neuropathy in humans and experimental animals. Leptophos, a representative of this class, and its impurities were found to induce delayed neuropathy with relative potency as follows: desbromoleptophos > pure leptophos > technical leptophos > leptophos oxon. Only desbromoleptophos was found to be neurotoxic [36].

Sulfotep is a highly toxic impurity that may be present in trace quantities in chlorpyrifos, an organophosphorus insecticide of moderate mammalian toxicity. In many countries, the level of sulfotep is limited to 0.3 or 0.5 % maximum concentration. Monitoring data from Asia indicate that some re-

gional manufacturers may be producing chlorpyrifos with sulfotep concentrations as high as 17 % (K. D. Racke, personal communication).

3.1.2 Chlorinated dibenzodioxins and dibenzofurans

There is an extensive literature base on the toxicity of polychlorinated dibenzodioxins (PCDDs), polychorinated dibenzofurans (PCDFs), and related compounds [69–71].

2,3,7,8-tetrachloro dibenzo-*p*-dioxin (2,3,7,8-TCDD) is a PCDD that is extremely toxic on an acute basis. An oral LD_{50} of no more than 0.6 μg/kg body weight was reported for female guinea pigs, whereas various rat strains and Rhesus monkeys were approximately 10-fold less sensitive and mice and rabbits 100-fold less sensitive than the guinea pig. Lethal effects of PCDDs and PCDFs in mice and guinea pigs are accompanied by a drastic decrease in body weight (wasting syndrome), and congeners with chlorine atoms at the 2,3,7, and 8 positions are the most potent. Humans accidentally exposed to 2,3,7,8-TCDD or organic mixtures contaminated with 2,3,7,8-TCDD suffered from chloracne and related skin disorders. Various types of adverse effects are observed when animals are subchronically or chronically exposed to these compounds including decreased body weight, haematological effects, and pathological changes in liver, thymus, and other lymphoid tissues. 2,3,7,8-TCDD does not exhibit genotoxic properties, but does induce liver tumors in experimental animals.

Epidemiological data provides limited evidence that 2,3,7,8-TCDD is a carcinogen for humans [72]. PCDD and PCDF congeners are inducers of hepatic arylhydrocarbon hydroxylase. Binding to the cytosolic Ah receptor, translocation to the cell nucleus, and interaction with DNA may result in the expression of various phase I and II enzymes. Enzyme induction is correlated with the observed in vivo effects. Observed adverse effects include disturbance of hormone metabolism, immunotoxicity, and developmental and reproductive toxicity.

PCDDs and PCDFs may be present as 75 and 135 isomers, respectively (Fig. 4). PCDDs may be formed in several ways. For example, they may be formed from chlorinated phenoxyphenols, which are the impurities of chlorophenols used for the synthesis of phenoxy acetic acids. They may also form by hydrolysis of chlorobenzenes used to manufacture chlorophenols, or from chlorinated diphenyl ethers. In addition, they may be formed during exposure to ultraviolet radiation or pyrolysis.

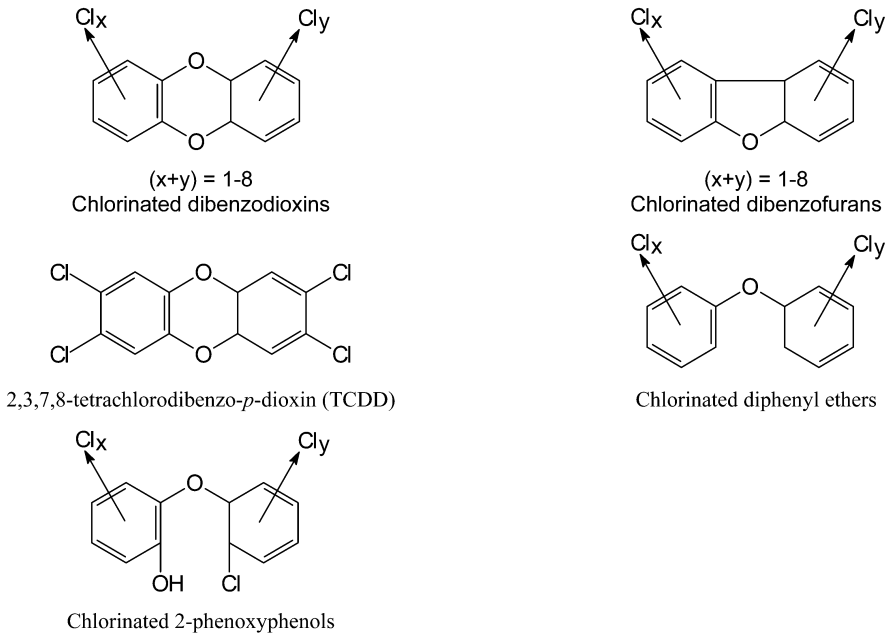


Fig. 4 General structural formulae of dibenzodioxins, dibenzofurans, and diphenyl ethers.

Dibenzofurans may be formed, for example, from diphenyl ethers or phenyldiols [42], which may be the impurities of chlorinated phenols. Dioxins may be formed during the manufacture of phenoxyacetic acid herbicides (e.g., 2,4,5-T, 2,4-D), pentachlorophenol fungicide, and the germicide hexachlorophene [73].

2,3,7,8-TCDD is the most acutely toxic member of the dioxin family. The reciprocal ratios of LD_{50} TCDD/LD_{50} 2,4,5-T are about 630 000 for guinea pigs and about 10 000 for female rats [31]. Levels of TCDD in technical 2,4,5-T were found to range from 0.1–55 mg/kg [7]. In the 1980s, much lower levels 10–80 μg/kg were reported. TCDD was also detected in pentachlorophenol at 1–21 μg/kg level. Pentachlorophenol and tetrachlorophenol samples were found to contain hexa- and octachlorodioxins at concentration of 1.7 to 647 mg/kg, as well as polychlorinated dibenzofurans, diphenyl ethers, and triphenyl ethers [43].

Although TCDD was not detected in 2,4-D ester and amine salt samples, some amine salts contained 2,7-dichloro-, 1,3,7-trichloro-, and 1,3,6,8/1,3,7,9-tetrachlorodioxins and an ester contained up to 23.8 mg/kg 2,7-DCDD [43]. Analogs of TCDD can theoretically be formed during the preparation of other pesticides as well (e.g., fenoprop, quintozene, dicamba, and chlorpyrifos) [6].

3.1.3 Chlorinated azobenzenes

TCAB (3,3′,4,4′-tetrachloroazobenzene), a structural analog of TCDD, has similar Ah receptor binding characteristics and causes similar adverse effects in rats [74]. Enhanced mortality of chicken embryos and malformations in embryos were observed, suggesting a teratogenic potency [75]. TCAB is a potent inducer of liver microsomal P450 in rats, and loss of body weight as well as changes in liver, spleen, and testis were observed [76,77]. Pharmacokinetic studies indicated that the compound is quickly cleared from the blood of rats (elimination half-life = 4 h), whereas the oral bioavailability was 30 % [78]. Extensive reduction of the azobond of TCAB to aniline derivatives may be observed, and these metabolites are rapidly eliminated from the body after sulfation and *N*-acetylation. TCAB was found as a contaminant in commercial samples of 3,4-dichloroaniline and in the herbicides diuron, linuron, and propanil, which are derived from 3,4-dichloroaniline. Agriculture Canada analyzed 23 samples of propanil for the presence of TCAB, and concentrations of the impurity were found to range from 1.1 to 30 mg/kg. The 10 mg/kg level was exceeded in 3 out of the 23 samples [26].

Hexachlorobenzene (HCB) was used as a fungicide, but it can also be formed as an impurity during synthesis of the herbicide dimethyl tetrachloroterephthalate (DCPA). HCB is also an intermediate in the production of pentachlorophenol (PCP). HCB causes photosensibility and skin disorders. It is mutagenic in *S. cerevisiae*, and treatment of hamsters resulted in the induction of thyroid tumors [79].

3.1.4 Nitrosoamines

An area of concern is the formation of *N*-nitroso-derivatives of pesticides, which may exhibit mutagenic and carcinogenic effects [79,80]. Over 70 % of nitrosated carbamate pesticides showed positive mutagenic effects using *S. typhimurium* strains, whereas less than 40 % of the nitrosated ureas yielded a positive response, highlighting important structure–activity relationships.

The compound *N*-nitrosodimethylamine (NDMA) is one such impurity of concern. The oral, inhalation, and intraperitoneal LD_{50} of NDMA in rats was reported to be 40, 37, and 43 mg/kg. Severe centrilobular necrosis in the liver is the major outcome of toxicity of NDMA in several species, including humans. An increase in fetal mortality was noted in rats exposed to NDMA either orally or by injection during gestation. No teratogenic effects were observed, however. The oral LD_{50} in rats of *N*-nitroso-*n*-propylamine (NDPA), a contaminant that may be found in trifluralin and isopropalin formulations, was 480 mg/kg, the s.c. LD_{50} was 487 mg/kg. There is sufficient evidence for carcinogenicity of NDMA in experimental animals [81,82]. Depending on the way of administration, NDMA may induce hepatocellular carcinomas and tumors of kidney and lung in exposed mice. In rats, tumors have been observed in kidney and bile duct, lung, liver, and nasal cavity, depending on the way of administration. There are no adequate data available on the carcinogenicity of NDMA in humans [81,83].

The secondary amines are the primary sources for the formation of nitrosoamines (Fig. 5). In addition, primary and tertiary amines as well as tetralkylammonium salts can form *N*-nitroso derivatives under the right conditions. Nitrosation of amines and amine derivatives (amides, ureas, carbamates, guanidines) can occur by reaction with nitrite and nitrogen oxides [49]. Several agricultural chemicals have been shown to contain a variety of *N*-nitroso derivatives. Ross et al. detected dialkylnitrosamines in commercial pesticide formulations ranging from 0.3 mg/l of NDMA in a sample of a home lawn care product to 640 mg/l in a sample of industrial herbicide that contained about 26 % of 2,3,6-trichlorobenzoic acid (TBA) formulated as the methylamine salt. The authors speculated that the NDMA might have been formed due to the addition of sodium nitrite as a rust inhibitor to the storage cans. These same authors also detected 154 mg/l of *N*-nitrosodipropylamine (NDPA) in a major agricultural herbicide containing trifluralin. NDPA is present in trifluralin by virtue of a side-reaction between nitrosating agents and dipropylamine during the amination step of the manufacturing process (Fig. 5). Several dinitroaniline herbicides and other compounds that utilize secondary amines for the manufacturing process have been shown to contain nitrosoamines [84].

Wigfield et al. [27] employed GC/TEA (thermal energy analyzer) for the analysis of commercial formulations of the mosquito repellent *N,N*-diethyl-*m*-toluamide (DEET), and the herbicide *S*-ethyl dipropylthiocarbamate (EPTC). These compounds are synthesized by using diethylamine (DEA) and di-*n*-propylamine (DPA), which are precursors of NDEA and NDPA, respectively. NDMA was detected in four of the 26 DEET samples (<0.05, <0.05, 0.05, and 0.14 mg/kg). The impurity NDPA (0.09–0.36 mg/kg) was found in all 6 of the EPTC formulations analyzed (0.09–0.36 mg/kg).

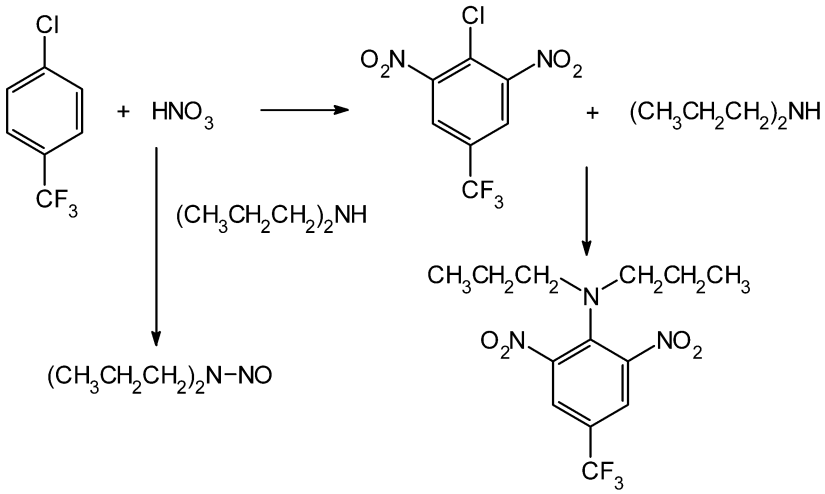


Fig. 5 Formation of *N*-nitrosodipropylamine during the synthesis of trifluralin.

3.1.5 Ethylenethiourea

Ethylene thiourea (ETU) is formed in the manufacture of EBDC pesticides such as maneb, mancozeb, metiram, and zineb. It can also be formed during prolonged storage or animal metabolism in these pesticides.

ETU exhibits moderate acute toxicity upon oral administration to rodents. The LD_{50} in mice and rats has been reported to be 3000 and 1832 mg/kg, respectively [85], and 545 mg/kg in pregnant rats [86]. Exposure to ETU induced enhanced numbers of micronuclei in mouse bone-marrow erythrocytes in the presence of nitrite [80]. In rodents chronically exposed to ETU in the diet, increased incidences of thyroid hyperplasia and thyroid follicular cell hyperplasia and increased liver weights have been observed. In an occupational study, reproductive or developmental effects were not observed in humans. ETU has been shown to be a potent teratogen in orally and dermally exposed rats, causing CNS and

skeletal abnormalities. Increased incidences of thyroid carcinomas and hepatomas have been observed in rats and mice orally exposed to ETU. A study of female workers occupationally exposed to ETU reported no increased incidence of thyroid cancers [82]. The 1993 JMPR [86] was able to recommend an acceptable daily intake for ETU in humans of 0.004 mg/kg body weight. ETU is thought to be the responsible agent for the thyroid toxicity associated with some of the EBDC pesticides.

3.2 Effects of impurities on physical properties of formulated products

The potential for high-volatility herbicides to cause damage to nontarget crops under certain conditions has long been recognized. Some ester formulations of the phenoxyacetic acid herbicides 2,4-D and 2,4,5-T are of concern because of the damaging effects of their vapors on sensitive plants. When an herbicide is to be used in the vicinity of susceptible crops, its official registration for such use will depend, among other things, on its low volatility. Low-volatility herbicide esters are sometimes contaminated by significant quantities of high-volatility esters, thus negating the crop safety of the low-volatility formulation. Such contamination could arise during manufacturing at the time of esterification if the high-molecular-weight alcohol raw material contained methanol or ethanol. Another possibility is that transesterification could occur during storage of the formulation if the formulation contained a short-chain alcohol. In one reported investigation, 2,4-D-isooctyl formulations, which are expected to be of low volatility, were rated as high volatility due to the presence of up to 238 g/l of 2,4-D-methyl ester [87].

The authors suggested a simple method for calculating the volatility of mixtures of active ingredients and contaminants, and concluded that a formulation should only be rated as low volatility if the herbicide vapor pressure is below 0.6 mPa at 25 °C. The volatility of the total formulation is especially important for ULV formulations because they are sprayed without dilution. As the spray droplets decrease in size due to evaporation, significant spray drift may result.

Particle growth of the pesticide binapacryl occurred at 30 and 45 °C in a suspension concentrate prepared with technical-grade and recrystallized binapacryl, respectively. No polymorphic change during the recrystallization could be detected. However, it was confirmed that the acceleration of particle growth in the suspension prepared with technical-grade binapacryl could be attributed to the presence of 4,6-dinitro-2-sec-butylphenol (DNBP), the major impurity in the technical material. The particle growth of binapacryl in aqueous suspension started at 30 °C when the technical material contained DNBP at or above 530 mg/kg and at 45 °C with DNBP content of less than 130 mg/kg. The authors concluded that DNBP existed mostly as fine particles in the medium. The melting point of DNBP (41.8 °C) was found to decrease to approximately 25 °C when it was mixed with binapacryl. Therefore, it was assumed that DNBP particles, which adhered to binapacryl particles, easily become a liquid phase and potentially accelerated the binding of binapacryl particles [15]. Similarly, a small amount (approximately 0.5 %) of a reagent used in the synthesis of the insecticide fenazaquin was reported to remain in technical-grade product after the purification step. This impurity migrated to the surface of the technical product crystals and reduced the melting point sufficiently for crystals to form clusters. This resulted in an increase in particle size. Suspension concentrates prepared from this technical material were unstable and exhibited poor biological efficacy. The material prepared by an alternative synthesis route, which avoided use of the offending reagent, was quite satisfactory [88].

3.3 Residue problems resulting from impurities

The insecticides dicofol or tetradifon may contain DDT and DDT-related compounds, which are much more persistent than either dicofol or tetradifon. Thus, use of formulations of these products containing DDT may result in residues in food exceeding the MRLs established for DDT, though DDT as such was not used. Impurity analyses of 38 dicofol formulations marketed by five companies was carried out in the United Kingdom during 1987 and 1991–92. The formulations manufactured prior to 1988 contained DDT-related impurities at concentrations up to 575 g/kg of dicofol. Formulations manufactured fol-

lowing the EC Prohibition Directive, requiring that DDT-related impurities represent less than 1 g/kg dicofol content, contained these impurities at levels up to 7 g/kg of dicofol [22].

Hexachlorobenzene (HCB) is an impurity in quintozene and chlorothalonil. Because HCB exhibits a much greater environmental persistence than quintozene, this impurity has been reported to constitute a much higher proportion of the aged residues in agricultural commodities than in either the technical material or the residues present upon application [89]. A similar problem may be observed when chlorothalonil is used.

Sulfotep, a highly toxic impurity that may occur in diazinon, is more resistant to hydrolysis than diazinon. Therefore, it may become a residue of concern during waste disposal or degradation of spilled diazinon in soil and water where hydrolysis represents a major mechanism of diazinon detoxification. Sulfotep levels ranged from <0.01 % (nondetected) to 0.53 % of diazinon in various formulations from Canada [17] and 0.3 to 0.4 % in formulated product from Brazil [20]. Sulfotep has also been detected in commercial formulations of other organophosphorus pesticides such as coumaphos, chlorpyrifos, demeton, disulfoton, fensulfothion, parathion, phosalone, and terbufos [17].

4. SAFETY ASSESSMENT OF PESTICIDES

No manufactured chemical material is 100 % pure; each pesticide contains impurities, which may contribute to the overall toxicity of the manufactured product. In principle, the safety assessment of one particular batch of a crop protection product, including both active ingredient and impurities, may proceed without exact knowledge of its composition and identification of the chemical structure of all the relevant constituents. For example, a portion of this particular batch may be subject to appropriate toxicological tests. The findings of such testing would then apply to the entire product, active ingredient and impurities, with the assumption that each chemical entity in the product may contribute to the overall toxicity observed. Consequently, when the toxicity of a different batch is assessed an increased or decreased toxicity may be observed if the proportion of a toxicologically significant impurity increased or decreased, respectively. Because the uniformity of manufactured batches cannot be accurately monitored and controlled without knowledge of the product composition, this type of composite testing approach is not acceptable. This is because the toxicological knowledge gleaned by testing one batch may not be transferable to subsequently produced batches. Therefore, three steps are essential for putting both the manufacturer and the regulatory agency in the best position for ensuring that unforeseen changes in the production process or the starting products do not occur. First, the identity and chemical structure of the impurities must be elucidated. Second, this information must be employed for the development of analytical methods for detection and quantification of impurity levels. Third, these methods must be employed in a quality-monitoring program associated with the manufacturing and formulation process for the pesticides involved.

A lack of attention to these steps will yield an incomplete safety assessment and may result in unknown hazard to workers handling (producing, shipping, storing, spraying, assessing residues in food) crop protection products. The theoretical evaluations [6] have demonstrated that dozens or even hundreds of specific compounds may be present as impurities in technical-grade pesticides at levels above 1 mg/kg. Most countries with advanced registration systems require the positive structural characterization of impurities present in technical pesticide products at or above the 1 % level. Impurities that may be present between 0.1 and 1 % may be identified based on their spectra and chromatographic properties. Because the structural characterization of unknown impurities is extremely difficult at less than 0.1 %, analytical efforts below this level may be justified only in those cases where evidence exists concerning the presence of a highly toxic or environmentally relevant contaminant (e.g., sulfotep, HCB).

The toxicological significance of the impurities associated with an active ingredient is essentially accounted for if these impurities are present in the tested product (generally, the technical-grade product; for specific tests the formulation as well) actually used in the toxicological investigations. The FAO/WHO has developed a set of principles for the characterization of the identity, purity, and stabil-

ity of test materials [90]. Thus, the regulatory assessment of the safety of a crop protection product is based on the assumptions, that the material produced during large-scale, commercial manufacturing has an equal or higher content of active ingredient and contains the same or fewer impurities at equal or lower concentrations as the fully characterized technical product which was used in the toxicological tests. This ensures that the human and environmental risks associated with manufacturing, handling, and use of the commercial product will not exceed those estimated during the earlier safety evaluations, which were based on testing of a representative batch of the product (e.g., pilot plant, laboratory synthesis).

This assumption may not be consistently satisfied with generic pesticides, which being no longer protected by patents may be produced by any manufacturer under varying quality-control programs. Once a pesticide is being manufactured by several or many producers, the resulting price competition places a premium on the minimization of manufacturing costs (e.g., quality assurance, safety testing). Thus, generic manufacturing processes may only focus on assay of the active ingredient content of the technical material and not consider levels of impurities to meet the full specification. In these instances, the amount of lower-quality technical material used in the formulation may merely be adjusted so as to produce a formulated product within the specified limits of active ingredient.

The results of analysis of commercial products indicate that, not only may impurity levels be different from those in the original technical product, even the active ingredient content and physical properties of these generic products may often not meet the specification. One example is provided by a survey of 348 samples obtained by GTZ (Deutsche Gesellschaft für Technische Zusammenarbeit GmbH) from 21 developing countries in Latin America, Africa, and Asia during 1989 to 1994. On average, the active ingredient content of more than one-third (34 %) of the tested products did not meet the FAO specification [91]. A similar frequency of occurrence of out-of-specification products has been reported following other extensive studies carried out in Costa Rica (29 % of 408 samples), Panama (28 % of 254 samples), Madagascar (56 % of 655 samples), El Salvador (28 % of 71 samples), and Malaysia (18–37 % of 396 samples) [92–94]. Another example is provided by the case of 2,4-D, which may contain the toxicologically significant impurity 2,4-dichlorophenol (2,4-DCP). The FAO guideline has established an upper limit of 3 g/kg of free phenol for 2,4-D. However, analyses of 2,4-D products imported into Vietnam from a generic producer in China revealed 2,4-DCP concentrations of between 14 and 23 g/kg. In contrast, no detectable residues of 2,4-DCP were found in comparable product imported from a basic manufacturer in New Zealand [50]. Except for ETU, there is no published information available on impurities of pesticide products manufactured and formulated in developing countries. These situations arise because generic technical products are often registered without appropriate characterization of impurities (i.e., to determine comparability with the original product evaluated) or toxicological testing (i.e., when comparability is not sufficient). The registration may be granted based on the misuse of evaluations carried out by the FAO/WHO Joint Meeting on Pesticide Resides (JMPR) or misinterpretation of FAO Specifications for Plant Protection Products.

The JMPR performs the toxicological and residue evaluations of pesticides required to provide scientific rationale for the establishment of maximum residue limits (MRLs) by Codex to facilitate international trade of agricultural products. The JMPR determines the acceptable daily intake (ADI) of pesticide residues by taking into account the appropriate safety factors (usually 10 for intra- and 10 for inter-species variability) and toxicological end points derived from various toxicological studies. These evaluations place a much greater emphasis on the active ingredient and metabolites that may be formed in plants or animals since these latter are generally present at concentrations several orders of magnitude higher than impurities found in the active ingredient. Currently, the only compound in the Codex list where the ADI specifies a limit on an impurity is quintozene. Due to the objective of the JMPR evaluations, to establish MRLs for dietary items, the toxicological evaluations are not as relevant for the assessment of occupational safety. The safety assessment for handlers and applicators of pesticide products must also account for the composition (i.e., impurities, coformulants) and stability of the commercial product as well as the circumstances of potential exposure method (e.g., method of appli-

cation, required protective clothing). Therefore, the JMPR evaluations for residues in food are not sufficient for assessing the safety of a compound, and they should not be used alone for granting registration of a pesticide containing the same active ingredient.

The FAO regularly publishes the FAO Specifications for Plant Protection Products. The specifications are based on the confidential information regarding the composition and physical/chemical properties of the product(s) provided by the basic manufacturer(s). Because the impurity profile may reveal proprietary details of the manufacturing process, details regarding impurities are included in the specifications only in a few cases. Furthermore, due to the past policy of FAO, the commercial name of the pesticide and identity of the manufacturer was not reported in the specifications published prior to 1999. This has led to the unsubstantiated conclusion by some authorities that all products containing the active ingredient within the specified range and having the specified physical parameters are essentially equivalent. Consequently, the registration requirements of many countries are satisfied if a pesticide, regardless of its manufacturing process and composition, complies with the FAO specification. No further information on the identity and level of impurities or stability of the formulation is required. The deficiencies of the FAO specifications published before 1999 have now been widely recognized, and the new procedure identifies the manufacturer(s), the products and their relevant impurities [3].

The previous examples highlight the firm linkage that exists between the specification of a crop protection product and the corresponding body of toxicological information. The specification should include the minimum concentration of the active ingredient and the maximum concentration of each relevant impurity. The safety assessment cannot be automatically transferred to product batches that are manufactured with different processes and from different starting materials, and that may have different impurity profiles from those of the product originally evaluated. If these factors are not taken into consideration during the safety evaluation of a product, adequate margins of safety for humans, nontarget wildlife, and the environment may not be maintained, and poisoning or contamination may occur. Similar problems may arise if authorization is given for the use of pesticides, stored for too long or under poor conditions, with application rates increased to compensate for the decreased active ingredient content.

4.1 Information required for safety assessment of pesticides

Requirements for the registration of pesticides are usually specified in national laws and regulations. However, these requirements and the thoroughness of registration assessments vary greatly between countries. The minimum information to be provided by all manufacturers (i.e., registrants) and suggested actions to be taken by the responsible authorities that are necessary for an adequate safety evaluation for a pesticide are briefly summarized below:

A. Information and materials required for characterization of the composition of technical products
   1. Detailed information on the manufacturing process, toxic impurities and potential precursors of toxic impurities in raw materials.
   2. Typical composition of the technical product (certified by a qualified laboratory in case of manufacturers where appropriate internal quality control system is not in place) including positive identification of major (≥1 %) and all toxicologically or environmentally relevant impurities and characterization of minor impurities (>0.1 %).
   3. Analytical methods suitable for monitoring of batch-to-batch uniformity of technical-grade product, including "fingerprint" chromatograms indicating the relevant impurities, UV–vis, IR, NMR, and MS spectra with assignments.
   4. Analytical procedures and standards to determine the relevant impurities.
   5. Reference sample of a typical batch of technical-grade material.

B. Information for the toxicological assessment of generic pesticides
   1. Certificate(s) of the original manufacturer on the composition of technical product(s) used for toxicological evaluations.
   2. Comparison of the composition of the technical product used for toxicological evaluations with that manufactured by a different procedure or under different conditions. The composition of the new and original product is comparable if the active ingredient content in the technical-grade product is equal to or higher and the concentrations of relevant impurities are equal or lower than they were in the original product that had been used for the complete toxicological tests. The composition is not comparable if a relevant impurity occurs in the new product, but not in the original product.
   3. The toxicological results may be accepted if the composition of the products is comparable.
   4. Additional toxicological studies are required if comparability cannot be confirmed.

C. Actions by the pesticide quality control laboratory of the government
   1. Frozen storage of the reference technical material submitted for registration in several small containers for future comparison.
   2. Evaluate impurities in imported batches of technical materials before formulation. Compare "fingerprints" obtained with suitable chromatographic and or spectrometric methods. Determine relevant impurities if suitable instrumental techniques are available.
   3. Notify the registration authority or initiate appropriate official actions if significant differences in the composition of the reference material and the sample are observed.

5. SUMMARY

There may be a substantial difference in the chemical composition of the technical-grade products of the same active ingredient manufactured under different conditions and from different raw materials. Alternative routes of synthesis often result in technical materials of different composition. These differences in impurity content may significantly affect the toxicological properties of pesticide products.

The chemical composition and purity of so-called "inert ingredients" used for formulating a pesticide such as carriers, solvents, surfactants, and adjuvants may affect the stability of the active ingredient. Furthermore, during extended storage degradation products may be formed, which pose toxicological hazards to handlers and applicators or dietary intake hazards to consumers of treated food.

For safety and efficacy assessment, in agreement with the principles outlined in the 5th edition of the *FAO Manual on Specification of Plant Protection Products* [3], "relevant" impurities are those that may exhibit pronounced toxic effects compared to the active ingredient, affect phytotoxicity and physical properties of formulations, result in undesirable residues in food, or cause environmental contamination.

Toxicological tests are usually carried out with the technical active ingredient considered to be of typical composition for the specific manufacturing process. The results of the tests are not necessarily valid for other technical materials of different composition or lesser purity. Similarly, toxicological data based on a particular formulated product cannot simply be extrapolated to other formulations consisting of different materials, because some of the "inert ingredients" may influence toxicity.

Determination of impurities, being present usually in the range of a few percent to 0.1 % (or less as in special cases such as TCDD, which is of interest at or below 0.01 mg/kg), is a very difficult analytical task, and may require the combined application of several analytical techniques such as GC/MS, GS/MS/MS, LC/MS, LC/MS/MS, GC/FTIR (Fourier transform infrared spectrophotometry), and high-resolution NMR. Such analytical techniques are not readily available in many laboratories carrying out quality control of pesticides.

The availability of a CIPAC or AOAC method for testing the active ingredient content of a pesticide is one of the preconditions for elaboration of an FAO specification. However, analytical methods and reference materials for impurities can generally be obtained only from the manufacturer. They are rarely readily available to regulatory laboratories, and this includes those impurities, which are included in FAO specifications.

Because of the commercial sensitivity of information related to the quality of pesticides, the results of quality control analysis are not published in many countries. However, the available information indicates that, even in countries with advanced registration processes and surveillance systems, the quality of pesticides does not always meet the specifications set in the registration document. The published literature, however, does contain examples that illustrate the need both for careful consideration of possible impurities at the time of registration of a pesticide and for development of systems for post-registration quality-control monitoring of marketed products.

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