LEVEL 1

Ziram

Statement of subject matter and purpose for which the monograph was prepared

1.1 Purpose for which the monograph was prepared (Document A)

This monograph is submitted to support the application for the first inclusion of the existing active substance ziram in Annex I to Directive 91/414/EEC, according to Commission Regulations (EEC) 3600/92 and 993/94.

1.2 Summary and assessment of information relating to the collective submission of dossiers (Document B)

Four companies notified of their intention to support the application for the inclusion of ziram in Annex I (UCB, Elf Atochem, FMC Foret and Bakelite Italia), two of which (UCB and Elf Atochem) formed a task-force.
From the time of notification up to now (1998), FMC Foret and the task-force UCB-Elf Atochem had a lot of contacts (meetings, letters) in order to form a common task-force. The contacts dealt with the sharing of study costs. At the end of 1997 FMC Foret joined the task-force UCB-Elf Atochem.

Nevertheless, since the companies did not reach an agreement before 30-10-95, date of submission of the dossiers, we evaluated the three applications separately in order to prepare the monograph of the active substance.

For additional information : see Annex C (C.2)

1.3 Identiy of the active substance (Annex IIA 1)

1.3.1 Name and address of applicant(s) for inclusion of the active substance in Annex I (Annex IIA 1.1)

As stated above, three dossiers were submitted to the Belgian authorities :

- The main dossier was submitted by a task-force, constituted by the 2 following notifiers :

Name	**ELF ATOCHEM AGRI SA**	**UCB SA**
Address	1, Rue des Frères Lumière Bp 9 - 78373 - Plaisir Cedex France	Pantserschipstraat, 207 9000 Gent - Wondelgem Belgium
Person to contact	B. SORNIN, Anne Marie JEAN	Mia LAGET
Telephone n°	+ (33) 1 30 81 73 00	+ (32) 9 254 14 11
Fax n°	+ (33) 1 30 81 72 51	+ (32) 9 254 14 10

The evaluation of the a.s. is totally based on this dossier as it was the most complete one.

- Two other dossiers were submitted by :

FMC Foret S.A. **Córcega 293** **08008 Barcelona** **Spain** **Person to contact : Ignacio Portabella** **Tel : 34 3 416 74 00** **Fax : 34 3 416 74 03**	**Bakelite Italia S.p.A;** **Via G. Mazzini 104,** **21058 Solbiate Olona** **Italy** **Person to contact: Dr. Alberto Coglio** **Tel : 39-331-355225** **Fax : 39-331-376390**

These 2 dossiers were incomplete. The available information was evaluated in the relevant sections (some toxicological data)

1.3.2 Manufacturer of the active substance (Annex IIA 1.2)

Manufacturer and contact point	
Elf Atochem Agri S.A. **1 rue des frères Lumière - 78373 Plaisir** **France**	**UCB S.A.** **Avenue Louise, 326 - 1050 Brussels** **Belgium**

Location of plants		
1	**Tankhoofd 10** **3196 KE Rotterdam** **The Netherlands**	**UCB Gent** **Pantserschipstraat 207 - 9000 Ghent** **Belgium**
2	**Aparto n°. 20** **22660 Sabiñanigo - Huesca** **Spain**	

1.3.3 ISO common name and synonyms (Annex IIA 1.3)

Ziram

1.3.4 Chemical name (Annex IIA 1.4)

IUPAC: Zinc bis (dimethyldithiocarbamate)
CA: (T-4) - bis (dimethyldithiocarbamato-S,S') zinc

1.3.5 Manufacturer's development code number (Annex IIA 1.5)

none

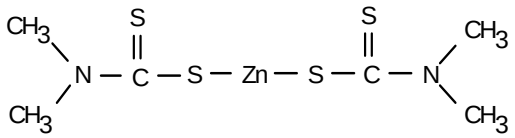
1.3.6 CAS, EEC and CIPAC numbers (Annex IIA 1.6)

CAS number : [137-30-4]
EEC number : 205-288-3
CIPAC number : 31

1.3.7 Molecular formula, molecular mass and structural formula (Annex IIA 1.7)

Molecular formula: $C_6 H_{12} N_2 S_4 Zn$

Structural formula:



Molecular mass: 305.81

1.3.8 Method or methods of manufacture (Annex IIA 1.8)

Confidential information, see Annex C

1.3.9 Specification of the purity of the active substance (Annex IIA 1.9)
1.3.10 Identity of inactive isomers, impurities and additives (Annex IIA 1.10)

It can be stated that the information submitted by the notifiers is not sufficient to establish purity limits and profile of impurities of technical ziram unequivocally. Additional information, including a complete analytical profile of batches, is required.

The minimum purity as stated by the notifiers within the task-force varies between 970 and 980 g/kg.
The minimum purity as stated in the FAO-specification for ziram technical (CP/82) equals 950 g/kg.

Confidential information, see Annex C

1.3.11 Analytical profile of batches (Annex IIA 1.11)

Confidential information, see Annex C

1.4 Identity of the plant protection products TRISCABOL 76 WG - ZIRAM 76 WG (Annex IIA 3.1; Annex IIIA 1)

1.4.1 Current, former and proposed trade names and development code numbers (Annex IIIA 1.3)

Trade name : **TRISCABOL 76 WG (Elf Atochem)**
ZIRAM 76 WG (UCB)

1.4.2 Manufacturer or manufacturers of the plant protection product (Annex IIIA 1.2)

Manufacturer and contact point	
Elf Atochem Agri S.A. **1 rue des frères Lumière - 78373 Plaisir** **France**	**UCB S.A.** **Avenue Louise, 326 - 1050 Brussels** **Belgium**
Location of plants	
1 **Tankhoofd 10** **3196 KE Rotterdam** **The Netherlands** **2** **Aparto n°. 20** **22660 Sabiñanigo - Huesca** **Spain**	**UCB Gent** **Pantserschipstraat 207 - 9000 Ghent** **Belgium**

1.4.3 Type of the preparation and code (Annex IIIA 1.5)

Physical state : Water dispersible granule (WG)

1.4.4 Function (Annex IIIA 1.6)

Fungicide, game and bird repellent

1.4.5 Composition of the preparation (Annex IIIA 1.4)

WG containing 760 g Ziram/kg

Other components : Confidential information, see Annex C

1.5 Uses of the plant protection products TRISCABOL 76 WG / ZIRAM 76 WG

1.5.1 Fields of use (Annex IIA 3.3; Annex IIIA 3.1)

Orchards, horticulture (ornamentals), game and bird repellent

Data to support the uses of Ziram as game repellent (trees and ornamentals) and as bird repellent (maize seed) were not submitted by the notifiers. Therefore the evaluation was restricted to foliar spray on fruit crops and ornamentals.

1.5.2 Effects on harmful organisms (Annex IIA 3.2; Annex IIIA 3.2)

Contact action, fungitoxic action,
inhibition of numerous enzymes in the fungus resulting in subsequent inhibition of spore germination and mycelial growth

1.5.3 Summary of intended uses (Annex IIA 3.4; Annex IIIA 3.3 to 3.7, 3.9)

Table 1.5.3-1 Harmful organisms controlled by TRISCABOL 76 WG - ZIRAM 76 WG

Crops protected	**Pests controlled**	
Fruits - foliar spray		
Citrus	**Coelomycetes**	***Deuterophoma tracheiphila***
Pome fruit	**Loculoascomycetes** **Teliomycetes** **Coelomycetes**	***Venturia spp.*** ***Gymnosporangium spp.*** ***Pezicula spp.*** ***(Gloeosporium-storage rot)***
Stone fruit	**Teliomycetes** **Hemiascomycetes** **Hemiascomycetes** **Discomycetes** **Coelomycetes** **Coelomycetes** **Coelomycetes**	***Tranzschelia pruni-spinosae*** ***Taphrina deformans*** ***Taphrina wiesneri*** ***Monilinia spp.*** ***Coryneum beijerinckii*** ***=Stigmina carpophila*** ***Coryneum microstictum*** ***Fusicoccum amygdali***
Ornamentals - foliar spray		
Ornamentals	**Teliomycetes** **Teliomycetes** **Coelomycetes** **Hyphomycetes**	***Puccinia sp.*** ***Phragmidium sp.*** ***Septoria spp.*** ***Alternaria spp.***
Game and bird repellent		
trees, ornamentals		**hare, rabbit, bird, wild game**
maize seed treatment		**birds**

Table 1.5.3-2 Summary of intended uses of TRISCABOL 76 WG - ZIRAM 76 WG

Crop Disease	Country	Maximum rate per application (kg a.s./ha)	Maximum rate per season (kg a.s./ha)	Spray concen-tration (g a.s./hl)	Maxi mum num-ber of applications per season	spray interval in days	Pre-harvest interval in days
Apple Scab *(Venturia inaequalis)*	**All Europe**	**2.70**	**16.20**	**94 to 270**	**6 (treatments against *Gloeosporium* included)**	**7-14 days - First application on young leaves**	**14**
Apple *Gloeosporium*	**All Europe**	**1.18**	**(rate already taken into account in the Venturia applica-tions)**	**75 to 118**	**4**	**7-14 days - First application half June**	14
Pear Scab *(Venturia pirina)*	All Europe	2.70	16.20	94 to 270	6 (treatments against *Gloe-osporium* included)	7-14 days - First application on young leaves	14
Pear *Gloeosporium*	All Europe	1.18	(rate already taken into account in the Venturia applica-tions)	75 to 118	4	7-14 days - First application half June	14
Medlar Scab *(Venturia inaequalis*)	All Europe	2.35	7.05	235	3	7-14 days - First application just before blooming	28
Cherry *Stigmina carpophila, Monilinia spp. Venturia cerasi*	All Europe	3.04	9.12	133 to 304	3	7-14 days - First application before/during flowering	10
Plum Rust *(Tranzschelia pruni-spinosa*) *Stigmina carpophila Monilia spp.*	All Europe	3.04	9.12	114 to 304	3	7-14 days - First application before/during flowering	10
Almond *Taphrina deformans*	South-Europe	1.78	5.34	133 to 178	3	7-14 days - Winter/Spring	14

Crop **Disease**	**Country**	**Maximum rate per application (kg a.s./ha)**	**Maximum rate per season (kg a.s./ha)**	**Spray concen-tration (g a.s./hl)**	**Maxi mum num-ber of applications per season**	**spray interval in days**	**Pre-harvest interval in days**
						treatment; First application on very young foliage	
Almond *Fusicoccum amygdali*	South-Europe	1.78	5.34	133 to 178	3	7-14 days - Autumn/ Winter treatment after harvest	14
Almond *Monilinia spp. Coryneum*	South-Europe	2.70	8.1	133 to 270	3	7-14 days - First application when disease occurs	14
Apricot *Monilia*	South-Europe	2.70	10.80	152-270	4	7-14 days Winter/Spring treatment; First application on young foliage;	14
Apricot *Coryneum beijerinckii*	South-Europe	1.52	6.08	114 to 152	4	Autumn/ Winter treatment after harvest	-
Peach *Taphrina deformans Stigmina carpophila Monilinia spp.*	All Europe	3.04	9.12	133 to 304	3	7-14 days Winter/Spring treatment; First application on young foliage NL: Application before flowering. ?	14
Peach *Coryneum beijerinckii (Stigmina carpophila) Fusicoccum amygdali*	All Europe	3.04	6.08	114 to 532	2	Autumn / Winter treatment after harvest	-
Ornamentals Outdoor Rust (*Puccinia*	All Europe	1.60		179 to 225	as needed	7 days - First application when disease	-

Crop Disease	Country	Maximum rate per application (kg a.s./ha)	Maximum rate per season (kg a.s./ha)	Spray concen-tration (g a.s./hl)	Maxi mum num-ber of applications per season	spray interval in days	Pre-harvest interval in days
spp,Uromyces dianthii) Black spot (*Diplocarpon rosae*)						occurs	
Game and bird repellent							
Trees Hare-Rabbit-Wildgame repellent	**-**	**-**	**-**	**160 to 320**	**1**	**Brush over trunk of the trees**	**-**
Ornamentals Birds-Rabbit-Hare repellent	**-**	**3.00**	**-**	**10 to 15**	**as needed**	**-**	**-**
Maize Bird repellent	**-**	**0.200**	**0.200**	**-**	**1**	**seed treatment**	**-**

1.5.4 Information on authorizations in EU Member States (Annex IIIA 12.1)

See Annex B, Appendix A - Authorizations and registrations

LEVEL 2

Ziram

Reasoned statement of the overall conclusions drawn by the Rapporteur Member State

2.1 Identity

The information provided by the notifiers is not sufficient to establish purity limits and profile of impurities of the technical a.s. unequivocally :

- the minimum purity stated by the notifiers within the task-force varies between 970 and 980 g/kg, which exceeds the min. purity of 950 g/kg as mentioned in the FAO-specification for technical ziram (CP/82 dd. 1979). However, as none of the notifiers submitted an acceptable analytical profile of batches, these values still remain to be confirmed.
- with regard to impurities, the notifiers did not address the possible occurrence of arsenic in technical ziram. Compliance of the technical a.s. with FAO-specification CP/82, which indicates a maximum content of 250 mg/kg arsenic, could thus not be fully evaluated.
- the technical specification of ziram should include the impurities (e.g. tetramethylthiourea) which are considered to be of toxicological significance. Supporting batch analysis data (incl. validated analytical methods) remain to be provided, in order to confirm the stated max. concentrations.

Additional information, including a complete analytical profile of batches, is required (see Level 4).

2.2 Physical and chemical properties

Active substance :

With the exception of the studies on hydrolysis and photolysis, only summary reports or data taken from literature (*) were provided to address the relevant Annex II points, which makes it impossible to adequately evaluate the results. Moreover, in most cases the purity of the test substance used was not sufficiently specified. Full reports containing all the necessary details on the test material and methods used thus remain to be provided (see Level 4). With respect to appearance of purified a.s., quantum yield of direct phototransformation, dissociation constant (pKa), estimated photochemical oxidative degradation, flammability, surface tension and oxidizing properties, data requirements were either not met or the prescribed test guidelines were not followed. The corresponding studies thus remain to be submitted (see Level 4).

The physico-chemical properties of the active substance can be summarized as follows :

Molecular weight	: 305.81
Melting point range *	: *further information required*
Appearance	: colourless powder with no characteristic odour (TC) *information on appearance of purified a.s. required*
Relative density *	: *further information required*
Surface tension	: *information required*
Vapour pressure	: *further information required*
Henry's Law constant	: *further information required*
Solubility in water	: *further information required*
Solubility in organic solvents	: *further information required*
Partition coefficient (log P_{ow})	: *further information required*
Hydrolytic stability (at 25 °C)	: DT_{50} (pH 5) = 10.4 min DT_{50} (pH 7) = 17.7 h DT_{50} (pH 9) = 6.3 d

Dissociation constant	: *information required*
UV/VIS absorption (max)	: *further information required*
Photodegradation (at 25 °C)	: DT_{50} (pH 9) = 8.7 h
Quantum yield	: *information required*
Flammability	: *further information required*
Auto-flammability	: *further information required*
Explosive properties	: *further information required*
Oxidizing properties	: *further information required*

The hydrolytic rate of degradation is pH-dependent, indicating that hydrolysis should play a very significant role in the environmental dissipation of the molecule under neutral or acidic soil and water conditions, while it will be somewhat slower under basic conditions. Photodegradation is significant in pH 9 buffered solutions.

Formulations :

A water dispersible granule (WG) containing 760 g/kg ziram was selected by the applicants as the representative formulated product (TRISCABOL 76 WG - ZIRAM 76 WG). The provided information was however incomplete, so that it was not possible to establish whether the formulation complies with the relevant FAO-specification.
With respect to bulk density, nominal size range of particles, dust content and suspensibility of the formulation, the submitted reports contain insufficient information and in the first three cases apparently state only “provisional” results, while for wettability and wet sieve test the findings mentioned in Tier I were not substantiated with a report. In order to be able to adequately evaluate the results in question, full “definitive” reports thus remain to be provided (see Level 4).
With respect to explosive properties, oxidizing properties, flammability/autoflammability, accelerated storage stability, shelf life, persistent foaming, dispersibility and flowability, data requirements were either not met or the prescribed test methods were not followed. The corresponding studies thus remain to be submitted (see Level 4).

2.3 Details of uses and further information

Uses of the formulations containing ziram :
Ziram exhibits fungitoxic action and acts through inhibition of numerous enzymes in the fungus, resulting in subsequent inhibition of spore germination and mycelial growth.

The intended uses of ziram formulations are restricted to foliar spray applications on fruit crops (orchards) and ornamentals. The notifiers submitted no data to support the use of ziram as game repellent (trees and ornamentals) and bird repellent (maize seed).

Detailed information is given under point 1.5 of this document.

Packaging :
The available packaging material was described and data on the testing of packaging suitability were submitted.

Procedures for cleaning application equipment and protective clothing :
The equipment is cleaned by rinsing several times with water, after which the rinsing water can be sprayed onto the field. No specific recommendations were given regarding the cleaning of protective clothing.

Re-entry intervals, waiting periods and other precautions to protect man, livestock and the environment

PHI : pre-harvest intervals as proposed for the intended uses are the following:
almonds : 14 days;
apples, pears : 14 days;
medlars: 28 days;
peaches, apricots :14 days;
plums, cherries : 10 days.

Re-entry periods : The point 'worker exposure' should be addressed by the notifier.

Ziram is not to be used with formulation containing copper or immediately after treatment with copper formulation.

Recommended methods, precautions and handling procedures to minimize the risks relating to warehouse storage, user level storage, transport, fire :

- Handling precautions : Keep the product in the original container, away from food, animal foodstuffs and out of the reach of children. Handle container tightly closed.
Anti-dust mask may be desirable when emptying bags. Wear suitable protective clothing and gloves, as well as eye/face protection.
Do not eat, drink or smoke during application. After treatment, wash and change clothes prior to anything else like eating, drinking or smoking.

- Storage : Store in a dry, cool, well-ventilated area.
Avoid exposure to direct sunlight.
Do not pile higher than 3 pallets.

- Transport: See Material Safety Data Sheets (Appendix B in Annex B)

- Fire-fighting measures:

Flash point :	not applicable
Auto-flammability :	no accurate information available
Explosive properties :	no accurate information available
Extinguishing media :	carbon dioxide, dry chemicals, foam (do not use water, except in case of an important fire)
Specific hazards :	Thermal decomposition may release toxic fumes

Special protective equipment for firefighters: in case of an important fire, use a self contained respiratory apparatus and protective clothes.

Procedures for use in the event of an accident during transport, storage or use :

- Environmental precautions : Stop any eventual leakage. Do not reject spilled product into sewers or natural water. Sweep up or vacuum to collect product without dust and incinerate according to regulation or recycle.

Information regarding methods for decontamination of water in case of an accident remains to be provided (see Level 4).

- Personal precautions : Avoid contact with eyes and skin. In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. In case of contact with skin, wash immediately thoroughly with soap and water.

In case of ingestion, give plenty of water and induce vomiting. In case of inhalation, move to fresh air, sit in upright position and loosen clothes.(first-aid measures : see also points B.5.9.4 and B.5.9.5)

Procedures for destruction or decontamination of the formulations and their packaging :

No specific recommendations. The preferred means to dispose of plant protection products containing ziram, their packaging and contaminated materials is through controlled incineration in a licensed incinerator. Information on pyrolytic behaviour is not required due to the absence of any halogen in the formulation.

2.4 Impact on human and animal health

2.4.1 Effects having relevance to human and animal health arising from exposure to the active substance or to their transformation products.

Absorption, distribution, metabolism and elimination :
In rats, Ziram is well absorbed from the gastro-intestinal tract, within 48 h after oral administration for 58-61% after a single low dose, for 60-69% after a single high dose and for 71-75% after a repeated low dose. Which means an overall oral absorption of 66%.

Partial inactivation, by a first-pass hepatic elimination, is suggested by the fact that, after inhalation, signs of systemic neurotoxicity were observed after 30 times lower doses than after oral ingestion.

After repeated exposure, recovery of radioactivity in tissues and carcass was low 7 days after exposure, suggesting that the compound does not accumulate.
In the dossier, metabolites were not identified and no metabolic scheme was proposed by the notifier. This point has to be addressed by the notifier. According to the JMPR (1996), Ziram is metabolized to dimethyldithiocarbamate and excreted as S-glucuronide conjugate. Other metabolic products include carbon disulfide, sulfate and dimethylamine .

The most important elimination route of the radioactive marker was via expired air (36 to 53% of the dose administered), the majority of which was expired during the first 48 h post-dosing. Urinary excretion represented 17% (high dose within 24 h) to 35% (repeated low dose within 24 - 48 h). Faecal excretion represented 9 to 18.5% and decreased with increasing the dose.

Acute toxicity:
Ziram is harmful when swallowed, and very toxic by inhalation. It is not a skin irritant but produces severe ocular lesions, skin sensitization may occur.

Based on the results of the FOB and motor activity evaluations, one or more parameters in each of the following functional domains were affected by a single oral administration of ziram at 300 and 600 mg/kg: autonomic, neuromuscular, sensorimotor, CNS activity and physiological. The neuromuscular and CNS activity domains appeared to have been slightly affected at a dose level of 15 mg/kg. It has been suggested that these neurotoxic effects might be due to the metabolite CS2.

Target organs, as indicated by macroscopic changes , are liver and lungs.

Table 2.4.1-1 : Summary of acute toxicity of Ziram

Type of test	Result	Purity (%)	Classification	Reference
LD50 oral rat1_ _ _+ _	381 mg/kg bw (227-594) 267 mg/kg bw (113-394) 320 mg/kg bw(176-422)	98.5% b.n°.8331A A	**Xn, R22**	Liggett and Allan, 1989a, task force study
LD50 skin rabbit	> 2000 mg/kg bw	98.5% b.n°.8331A A	-	Liggett and Allan, 1989b, task force study
LC50 rat, 4 h dust, whole body _ _ _+ _	0.08 mg/l (6.72 mg/kgbw*) 0.06 mg/l (5.04 mg/kg bw*) 0.07 mg/l (5.88 mg/kg bw*)	98.5% b.n°.8331A A	**T^+ R26**	Jackson and Hardy, 1989, task force study
LC50 rat, 4 h dust, nose only _ _ _+ _	0.18 mg/l (15.13 mg/kg bw*) 0.08 mg/l (6.72 mg/kg bw*) 0.13 mg/l (10.93 mg/kg bw*)	98.4%;lot n°.1208 AB/V609	**T^+ R26**	Blagden, 1991, task force study
LC50 rat, 4 h aerosol, nose only _+ _	< 0.2 mg/l (16.81 mg/kg bw*)	97.4%; lot n°.4/52019	-	Kieran, 1995, Bakelite
Skin irritation rabbit 4 h	not irritant	98.5%; b.n°.8331A	-	Liggett and McRae, 1990, task force study
Skin irritation rabbit 4 h	not irritant	97.4 %; b.n°.4/5201 9	-	Haynes and Brightwell, 1995a, Bakelite
Eye irritation rabbit	severe irritant	98.5%; b.n°.8331A	**Xi, R41**	Liggett and McRae, 1990b, task force study
Eye irritation rabbit	severe irritant	97.4 %; b.n°.4/5201 9	-	Haynes and Brightwell, 1995b, Bakelite
Skin sensitization guinea pig M&K	not a sensitizer	97.4 %; b.n°.4/5201 9	-	Haynes and Brightwell, 1995c, Bakelite
Split adjuvant test	sensitizer	99.04%, b.n°.8331 AA	**R43**	Daamen, 1988, task force study

* Approximate conversion from environmental concentration to dose inhaled, assuming a rat ventilation volume of 7 l/h during 4 h.

Genotoxicity:
Ziram, after metabolic activation, induced base-pair substitution in strain TA100 of *S. typhimurium*. A gene mutation test in mammalian cells was not supplied. This point has to be addressed by the notifiers . Ziram did not induce chromosome aberrations in CHO cells *in vitro*, and in mouse bone marrow cells and spermatogonia *in vivo*. It did not induce micronuclei in peripheral erythrocytes after sub-chronic exposure *in vivo*. In another study, ziram did not induce micronuclei in mice bone marrow after oral exposure. Ziram did not induce DNA repair activity in hepatocytes in culture.
In the open literature, positive results have been published based on different methods. The reliability of these results is, however, questionable. Therefore, our conclusions are based on test results obtained according to officially accepted test methods.
Ziram is not genotoxic.

Table 2.4.1-2 : Summary of genotoxicity of Ziram

Type of test	Result	Product, purity, batch number	References
***In vitro* genotoxicity tests:**			
Ames test TA1535, TA1537, TA1538,TA98 and TA100+/- S9	positive	98.5%; B.n°8331 AA	Jones et al., 1990 task force study
Gene mutation in mammalian cells	no data	-	-
Chromosome aberrations in CHO cells, strain K1-BH4	negative	98.5%; B.n°8331 AA	Brooker and Akhurst, 1989 task force study
UDS in rat hepatocytes	negative	98.5%; B.n°8331 AA	Proudlock, 1989 task force study
***In vivo* genotoxicity tests:**			
Micronucleus assay in mice peripheral blood (89 day, oral)	negative	98.8%; 8331AA	Proudlock and Taylor, 1992 task force study
Micronucleus assay in mice bone marrow	negative	97.4%;b.n° 4/52019	Ciliutti and Brightwell, 1995, Bakelite
Mouse bone-marrow chromosome aberration test (oral adm.)	negative	98.5%; B.n°8331 AA	Völkner, 1992a task force study
Chromosome aberration in mouse spermatogonia	negative	98.4%; b.n°.8331 AA/V528	Völkner, 1992b task force study
UDS *in vivo* using rat hepatocytes	negative	97.4%;b.n° 4/52019	Falezza and Brightwell, 1995, Bakelite

Short-term, repeated dose toxicity:

Ziram decreased in rats and mice, body weight gain, food intake and food efficiency. Dogs presented a subdued behaviour and/or unsteady gait, with slight alterations in body weight and food efficiency, increase in liver weight, they vomited and had diarrhoea.

In the rat, T4 serum level showed a dose related reduction, T3 and TSH were not significantly affected. Moreover, minor, but consistent, changes in biochemical parameters were observed (îtotal protein , albumin, Ca^{++}, RBC and ì **urea nitrogen, creatinine and MCHC).**

In the rat, the target organs were liver and kidneys, as shown by the presence of degenerative alterations. In mice, toxic effects were more diffuse and no specific target organ could be determined. Dogs showed an increased liver weight.

In the subchronic experiment (90 day study), the non-glandular stomach was the target organ, with minimal

epithelial hyperplasia in rats, and epithelial hyperkeratosis and minimal epithelial hyperplasia of the limiting ridge in the stomach of mice.
In dogs, the target organs were liver and spleen, with at the start increased pigmentation of Kupffer cells and/or macrophages with Perls'positive material, possibly reflecting increased iron metabolism and turnover. In dogs, also the following observations were made, a slight lowering of red cell indices, acute inflammatory cell infiltration in the lungs, decreases in heart weight.

In these studies (rat, mice, dog), the lowest doses administered already produced adverse effects, which were sometimes quite minimal but consitent with the observations made at higher doses.

In a 21-day percutaneous test, ziram affected the liver in rabbits. This effect occurred at 300 mg/kg bw/d. No dermal reactions were observed.

In contrast to the acute experiment, repeated dosing of ziram in the rat, at doses producing systemic toxicity, did not induce behavioural and neuronal toxicity. The toxicological significance of the moderate inhibition of brain NTE is not clear. Neurotoxicity, more especially OPIDN - organophosphate induced delayed neuropathy- has been linked to profound NTE inhibition , acompanied by ageing of the agent-enzyme complex.

Table 2.4.1-3 : Summary of the short-term toxicity studies of Ziram

Study	NOAEL mg/kg bw/day	LOAEL mg/kg/day	Critical effects	Purity, b.n°.	Reference
28 day , oral rat	**3**	**15**	î **body weight,** î food efficiency degenerative alterations in liver and kidney tubuli	98%; unknown batch	Dickhaus and Heisler, 1980 task force study
28 day , oral rat	<45.5	45.5	î body weight gain; ì **liver weight(r) ;î food consumption**	**98.5% 8331 AA**	**Chambers et al., 1992a task force study**
28 day , oral mice	**<374**	**374**	**î body weight gain, î food consumption, îheart weight,** î brain weight	98.5% 8331 AA	Chambers et al., 1992b task force study
28 day , oral dog	<25	25	vomiting, ì liver weight	98.5% 8331 AA	McLean et al, 1992a task force study
90 day , oral, rat	< 7.4	7.4	**ìBUN,î Ca^{2+} ,î blood proteins**	**98.7%; 8331 AA**	**Powell et al., 1992 task force study**
90 day , oral, rat (satellite group 104 wk)	**3**	**9.1**	î RBC, î blood protein, î **albumin,** ì **MCV**	**98.7%; b.n°.8331 A**	**Powell et al., 1994, Task force study**
90 days, oral, rat neurotox.	**systemic tox. :14 neurotox.: 34**	**34 -**	î mean brain neurotoxic esterase -	V528/8331 AA; 97.87%	Lamb, 1993 task force study
90 day , oral, mice	<15	15	î body weight gain, î food consumption, î spleen weight	98.7%; 8331 AA	Powell et al., 1993 task force study
90 day , oral, dog	4.07	12.15	liver necrosis, pigmented Kupffer cells	98.7%; 8331 AA	McLean et al, 1992b task force study
1 year , oral, dog	1.6	6.6	hepatocyte degeneration, inflammatory cell infiltration	8331AA, 98.5%	Smith et al., 1993 task force study

Study	**NOAEL mg/kg bw/day**	**LOAEL mg/kg/day**	**Critical effects**	**Purity, b.n°.**	**Reference**
21 day, dermal rabbit	100	300	ì **AST in females**	**98.5%: 8331 AA**	**Edwards et al;1989 task force study**

Long- term, repeated dose toxicity :

As in the short-term repeated dose experiments, long-term administration of ziram in rats produced decreases in body weight gain, food intake, and erythrocyte parameters suggestive of anemia.

Furthermore, rats showed the following treatment-related tissue changes: haemosiderin deposits in spleen and liver, cortical degeneration of adrenals (males), increased prominence of ultimobranchial cysts in the thyroid and C-cell hyperplasia (females), degenerative/atrophic skeletal muscles (males), axonal degeneration in spinal cord and sciatic nerves, adipose replacement of exocrine pancreas (males), lipofuschin accumulation in kidneys (females), bile duct hyperplasia in the liver, and hyperplastic and erosive lesions of the nonglandular epithelium in the stomach (males). Some of these changes already appeared at the lowest dose studied, 2.5 mg/kg bw/day and, therefore, the identification of a NO(A)EL was not possible.

At 24 mg/kg bw/d, male rats showed treatment-related haemangiomata in mesenteric lymph nodes and spleen. These haemangiomata were not pronounced, did not show evidence of malignancy and were confined to this group and sex only.

Studies from the open literature confirmed the ziram-induced muscular atrophy and sciatic nerve degeneration. Moreover, at doses higher than in the controlled studies, ziram was found to produce skeletal lesions and thyroid hypertrophy. In these studies the NOAEL was 0.7 mg/kg bw/d. In contrast to the well controlled study, one of the published studies showed that ziram, containing 6.5% of thiram known to produce C-cell hyperplasia and adenomas in female rats at the dose of 8 mg/kg bw/d, induced thyroid C-cell adenomas and carcinomas in male rats, statistically significant at a dose of 22 mg/kg bw/d. This observation might form a continuum with the C-cell hyperplasia seen in the well controlled study. In a similar study conducted on F344 rats, the incidence of C-cell hyperplasia was significantly depressed in males at 74 mg/kg bw/d. In this study, male and female rats, at 74mg/kg bw/d, showed enlargement of the thyroid associated with follicular hypertrophy.
The effects on the thyroid became critical in the assessment of ziram toxicity and further explanations will be needed to clear if ziram treatment may increase or decrease the proliferating lesions of C-cell in the thyroid.

In mice, ziram did not induce tumours at dose levels up to 82 mg/kg bw for 80 weeks. In all treated groups, increased incidences of centrilobular and/or generalised hepatocellular enlargement were seen. Urinary bladder epithelial hyperplasia was observed in males and females receiving 82 mg/kg bw and in males receiving 27 mg/kg bw. The NOAEL was lower than 3 mg/kg bw/d. Pulmonary tumours, found in one study, occurred in the presence of a virus infection which makes any interpretation difficult.

On the basis of the increased incidence of haemangiomata and thyroid C-cell hyperplasia, adenomata and carcinomata, a tumorigenic effect of high doses of ziram in the rat cannot be excluded. Since the overall conclusion with regard to mutagenicity is negative, the possible tumorigenic mechanism remains unclear.

Table 2.4.1-4 : Summary of long-term toxicity of Ziram

study	NOAEL mg/kg bw/d	LOAEL mg/kg bw/d	Critical effects	Purity (%) batch number	References
rat, 104 weeks, oral	< 2.5	2.5	skeletal muscle degenerative/atrophic changes, haemosiderin in spleen, adipose replacement of exocrine pancreas, cortical degeneration of adrenals, prominent ultimobranchial cysts in the thyroid, hyperplastic and erosive lesions of the stomach	98.7%; b.n°.8331A	Powell et al., 1994a, Task force study
mouse, 80 weeks oral	< 3	3	centrilobular enlargement, sometimes with vacuolation of hepatocytes reduced food consumption	98.7%; b.n°.8331AA	Powell et al., 1994b, task force study

Reproductive and development toxicity :

Ziram did not affect reproductive performance in the 2-generation rat study at the doses studied. Parental toxicity was observed in the F0 and F1 generations at the dose of 25 mg/kg bw (food concentration 540 ppm), e.g., inhibition of body weight gain and reduced food intake. At the same dose neonatal toxicity was expressed, e.g., slightly reduced pup body weights (F1 and F2).

Teratogenic effects, with regard to embryofoetal development and morphology, were not observed at doses that did not also produced maternal toxicity in rats. In rabbits, maternal toxicity was observed at 7.5 mg/kg bw/d but no teratogenic effects were reported.

From open literature, ziram has a low teratogenic effect that only becomes effective at dosages that are lethal to 50% of the mothers (100 mg/kg bw/d).

Table 2.4.1-5 : Summary of reproductive and development toxicity

Study	NOAEL mg/kg bw/d	LOAEL mg/kg bw/d	Critical effects	Purity (%) batch number	References
2 generations, oral, rat	**systemic maternal tox. : 10** **neonatal tox : 10** **reproduction : 25**	**25** **-**	**alteration of weight parameters.** **-**	**technical, lot V528/8331AA 97.8%**	**Nemec, 1996**
terato, oral, rat	**-maternal toxicity: 4** **- developmental: 4**	**16** **16**	**salivation, î food consumption,bw loss, retarded bw gain** **î mean foetal mean litter weight marginal ì visceral anomalies**	**technical, b.n°.8331 AA; 98.9%)**	**Smith et al., 1990** **task force study**
terato, oral, rabbit	**-maternal toxicity :3** **-developmental :7.5**	**7.5** **15**	**î bw gain, food intake and mean gravid uterus** îlitter and foetal weight, îcrown-rump length	technical, 98%, b.N°:Z-1461	Barker, 1986 task force study

2.4.2 Establishment of an Acceptable Daily Intake (ADI)

An ADI is proposed on the basis of long-term toxicity in rats or mice. In these studies, effects were seen at all doses, the LOAEL being 2.5 and 3 mg/kg bw/d respectively.
It is, however, probable that the NOAEL is not much lower since in a study from open literature, 1 mg/kg bw/d was a dose without adverse effect. We therefore, feel able to propose an ADI based on a LOAEL and an assessment factor of 1000.

ADI = 0.003 mg/kg bw/d

The same proposal was made by the JMPR (1996)

2.4.3 Establishment of an Acceptable Operator Exposure Level (AOEL)

An AOEL as an internal, systemic dose:

The systemic AOEL short-term for man is calculated on the basis of an NOAEL from a sub-chronic animal experiment, taking into account the apparent degree of absorption, and applying an assessment factor, chosen in function of the critical effect observed in the animal experiments.

It appears from the animal experiment that a subchronic exposure to 3.2 mg/kg bw/day (lowest NOAEL, taken from the rat 90 day oral study, satellite study of 104 week) of ziram will not result in any toxic effect. It further appears from the ADME studies that orally ingested ziram is absorbed at a level of 58-75.6% after low dose (single or repeated) within 48 h. Therefore, a correction factor of 50% was applied. An assesssment factor of 100 is proposed for the extrapolation to man.

The acceptable operator exposure level, expressed as an internal, systemic dose becomes:

AOEL short-term = 0.016 mg/kg bw/day

(The notifier proposed the 90 day dog and the 28 day rat studies with an assessment factor of 25, giving an AOEL = $\frac{3}{25}$ = 0.12 mg/kg bw/day).

An AOEL as a dermal exposure:

A 21 day dermal study exists in the rabbit, which would allow the calculation of a dermal AOEL.In this study a NOAEL = 100 mg/kg bw/d was reported . At the LOAEL ,systemic toxic effects were reported. Using an assessment factor of 100, this gives :

AOEL dermal = 1 mg/kg bw/day

2.4.4 Establishment of the drinking water limit

On the basis that exposure through drinking water should not account for more than 10 % of the ADI, assuming an average consumption of 2 l of water per person par day and an average body weight of 70 kg a limit of 0.01 mg/l is proposed.

$$MAC = \frac{ADI \times bw \times P}{C} = \frac{0.003 \times 70 \times 0.1}{2} = 0.01 \text{ mg/l}$$

MAC = maximum allowable concentration.

2.4.5. Impact on human or animal health arising from exposure to the active substance or to impurities contained in it.

On the basis of the toxicological data the health risks to animals and man of an acute exposure to ziram can be summarized as follows: it is harmful when swallowed, very toxic by inhalation, severe ocular lesions may occur as well as skin sensitization. Ziram induces point mutations *in vitro*, but is not genotoxic *in vivo*. After short-term or long-term exposure above the accepted exposure levels, lesions occur in the target organs, e.g., liver and kidneys. In rat and mice, the non-glandular stomach was also affected. Reproductive performances were not affected . Ziram is not teratogenic.

Health risk for humans:
According to the dossier, no epidemiological studies are available concerning human exposure to ziram. No major exposure accidents of the general population have been reported up to date.
Workers with severe skin diseases, especially eczema or allergic dermatitis, should avoid exposure to dithiocarbamates, known as common skin sensitizers and irritants.
In view of the inhibitory effect of dithiocarbamates on ethanol hepatic metabolism, persons with alcohol problems should be carefully considered before employment at work where they could be exposed to these substances. After alcohol ingestion, exposed individuals may experience adverse reactions, such as flushing. Subjects with disorders of thyroid or kidney function should also be carefully evaluated before employment at workplaces where significant exposure to dithiocarbamates is possible(Liesivuori and Savolainen, 1994).
According to the dossier, no human data concerning toxic effects following the use of preparations containing ziram are available. There seems to be no risk for adverse health effects for consumers. There was also no evidence of bioaccumulation .

Exposure resulting from the application of formulations containing Ziram:

Risk for the operator:
Ziram 76 WG is used as foliar fungicide for protecting fruit trees. According to the German exposure model, or to the UK model, operator exposure with or without PPE is not acceptable for tractor orchard sprayers (3.04 kg a.s./ha).

Actual exposure of mixer/loaders and applicators to Ziram 76 WGD fungicide applied by ground equipment in orchard crops was measured: apple orchards were sprayed using typical airblast sprayers pulled by open-cab tractors or tractors with no cabs; sprayers were loaded using typical open-pour loading equipment. In this study 3 mixer/loader and 3 applicators were controlled.
An evaluation of the acceptability of the operator exposure under the intended uses conditions of the EU was performed taking into account the results of this actual exposure study.
With a use rate of 3.04 kg/ha and 30 ha treatment a day, exposure reaches 36.5 µg/kg bw/day with PPE and 61.2µg/kg bw/day without PPE which represent 225 and 383 % respectively of the AOEL. The use of an half-mask with combination filter A1P2 may reduce the important contribution of the inhalation exposure. When gloves and a mask are used, exposure is below the AOEL (88%) and therefore acceptable.

Risk for the bystander:
Considering a spray drift of 4.5% (Ganzelmeier, 1992), dermal exposure of a bystander represents approximately 28% of the dermal AOEL ; by inhalation, exposure accounts for 2% of the AOEL systemic. The risk for the bystander is therefore acceptable.

Risk for the worker:
<u>This point should be addressed to the notifier.</u>

Human exposure resulting from ingestion of residues:

Risk for the consumer:
The risk for the consumer cannot be at this stage completely assessed.<u>The plant and animal metabolism studies have failed to give information on the nature of intermediary degradation products to which the consumer could be exposed.</u>

Considering that residues of toxicological significance are ziram and its metabolites containing the intact CS_2 moeity, it has been calculated that the IEDI is acceptable for an average consumer on the basis of the intended GAPs and of the FAO/WHO European diet. The intake of residues by extreme consumers of pome fruits may however exceed the ADI.

2.5 Methods of analysis

2.5.1 Analytical methods for analysis of the active substance as manufactured

The methods submitted allow to determine the purity, the impurities and the additives of the technical a.s., although some additional validation is required with regard to relevant impurities (e.g. tetramethylthiourea) . The method for the determination of pure a.s. in the a.s. as manufactured is the officially accepted CIPAC 61/1/M/1.2 method, with only some minor modifications to the apparatus and reagents. As this method determines the a.s. via the carbon disulphide content, it is not specific for ziram but also measures CS_2-containing impurities (if present in the technical ziram).

2.5.2 Analytical methods for formulation analysis

The method submitted for the determination of pure a.s. in WG-formulations is the officially accepted CIPAC 31/WG/M/3 method, with only some minor modifications to the apparatus and reagents. The comment made under point 2.5.1 with respect to the specificity of method CIPAC 61/1/M/1.2 also applies to this method.

For the determination of relevant impurities in plant protection products, the notifier refers to the methods that were submitted for the determination of impurities in technical a.s.. Validation data demonstrating the applicability of these methods to WG-formulations were however not provided.

No methods are required for the determination of formulants in the plant protection products, since none of the formulants are considered to be of toxicological or environmental significance

2.5.3 Analytical methods for residue analysis

Feed and food of plant origin :
The analytical method (CS_2-evolution + spectrophotometry) submitted for the determination of ziram residues on crops, being based on CS_2-evolution, measures all dithiocarbamate residues and thus allows no selective determination of ziram. Validation data were not provided .
A selective method of analysis is needed. Ziram has indeed a particular low ADI in comparison with other dithiocarbamates, requiring specific residue levels.

Feed and food of animal origin :
Methods for the determination of residues in food matrices of animal origin are not required since residues of ziram are not expected in animal products for human consumption.

Soil, water, air :
The analytical method (Zn-complexation + spectrophotometry) submitted for *water* analysis allows the selective determination of ziram residues, but additional validation is required in order to ascertain, among other things, if for drinking water a LOQ of at least 0.1 µg/l (= EU drinking water limit) can be obtained.

The analytical method (CS_2-evolution + GC-ECD) submitted for the determination of ziram residues in *air*, being based on CS_2-evolution, measures all dithiocarbamate residues and thus allows no selective determination of ziram. Additional validation data are required.

The applicant submitted no methods for *soil* analysis. Validated analytical methods that allow the determination of ziram and/or relevant metabolites in soil remain to be provided.

Body fluids and tissues :
The analytical method (CS_2-evolution + spectrophotometry) submitted for the determination of ziram residues in milk, urine, tissues and feces, being based on CS_2-evolution, measures all dithiocarbamate residues and thus allows no selective determination of ziram. Additional validation data remain to be provided.

2.6 Definition of the residues

2.6.1 Definition of the residues relevant to MRLs

Plant products
The proposed residue definition is ziram. It is necessary to set specific MRLs for ziram due to its higher toxicity than other dithiocarbamates.

Animal products
As residues of ziram or CS_2 in animal tissues are not expected, neither a residue definition nor MRLs are needed.

2.6.2 Definition of the residues relevant to the environment

The proposed residue definition are
Residue in soil : ziram
Residue in water : ziram, dimethyldithiocarbamic acid, dimethyldithioformamide, dimethylformamide

2.7 Residues

2.7.1 Residues relevant to consumer safety

Provisionally (a complete information about the metabolism in plants is not yet available) the residue relevant for consumer safety may be considered as being the parent compound and the metabolites with the intact CS2 moiety.
The ratio between residues relevant for MRLs and those relevant for consumer safety is not known.

2.7.2 Residues relevant to worker safety

The proposed residue definition is ziram.

2.7.3 Proposed EU MRLs and compliance with existing MRLs

2.7.3.1 Proposed EU MRLs

None as the method of analysis according to the residue definition is not available.

2.7.3.2 Compliance with existing MRLs

No existing MRLs.

2.7.4 Proposed EU import tolerances and compliance with existing import tolerances

None

2.8 Fate and behaviour in the environment

2.8.1 Fate and behaviour in soil

Route of degradation :
Under aerobic conditions, after cleavage of the molecule to dimethyldithiocarbamic ions, 1,1-dimethylurea is formed. Final metabolites of ziram are CS_2 + CO_2 (48.35% after 60 d) and bound residue (max 48.16 % after 7 d, 42% after 60 d).
DT_{50} of 41.9 hours (1.7 days) was calculated for ziram.
Information on the properties of 1,1-dimethylurea should be provided.

In the photolysis study, DT_{50} of 8-8.9 hours and 20-16.2 hours were calculated respectively for irradiated and dark samples. **In addition to ziram, 10 photodegradates were detected. Due to presence of artifacts, clear photolysis pathway cannot be proposed.**

Rate of degradation in the lab - Dissipation in the field :
Rate of degradation should be determined in 3 other soils at 20°C and in one soil at 10°C.

Soil dissipation studies are ongoing. Preliminary information indicates that the DT50 is 5-6 days. Final results should be provided.

Adsorption, desorption :
According to Mc Call (1988) , ziram exhibits slight mobility to immobility in the soil. (Koc = 314-12010). The stability of ziram should be determined. The role of organic matter in adsorption and hence use of Koc is questionable when considering the Koc range obtained.

Column leaching :
Two studies with fresh and aged residue were performed. The a.s. has low mobility. 6.6-14.3% of the radioactivity were recovered in the leachate. The characterization of the radioactivity recovered in the leachates should be provided.

Lysimeters :
Not submitted, not necessary.

PEC soil :

At this stage, due to the lack of data, it is only possible to calculate an initial PEC soil.

The following assumptions were made to calculate an initial PEC
- application rate of 3.040 kg a.s./ha in orchard
- 50 % of the deposit reaching the soil surface
- dispersion in a 5 cm soil layer
- soil density = 1.5 kg/dm^3

Initial PEC = 2.027 mg a.s./kg soil

The notifier should provide information on the PEC soil short term and long term after repeated applications for the a.s. and the relevant metabolites.

2.8.2 Fate and behaviour in water

Hydrolysis :
Ziram is not persistent in water at pH5 and pH7. Its major degradate is CS_2.
DT_{50} pH5 = 10.4 minutes
DT_{50} pH7 = 17.67 hours
DT_{50} pH9 = 6.31 days

At pH9 ziram is hydrolyzed with a DT_{50} pH9 = 6.31 days. The major degradate found at pH 9 was dimethyldithiocarbamic acid (DDC) (~ 75% after 30 days).

Phototransformation :
Ziram is rapidly photodegraded in water (DT_{50} = 8.66 hours) .
15 transformation products were observed in the 24 hour-duration of the study.
The two major degradates (Degradates A and E), which amounted to an average of 26.83 % and 20.59 % of the total radioactivity, were identified as sole N,N-dimethylformamide (!). Another major degradate (Degradate F) observed at an average level of 15.28 % was identified as N,N-dimethylthioformamide.
This study performed on the a.s. revealed the presence of several transformation products. It would be necessary to have more information about the fate and the effects of these metabolites in water (physico-chemical characteristics, persistence, effects on human and non-target organisms)

Ready biodegradability :
Not submitted. The study is required to decide whether the R53 phrase is applicable.

Water/sediment studies :
Not submitted. The study is required.

PEC surface water :

The estimations of the PECsw were calculated assuming that :
- DT_{50} = 18 hours (Hydrolysis rate at pH 7)
- Water layer = 30 cm
- Spray drift scenarios according to Ganzelmeier (1995)
- Degradation rate was calculated according to first order kinetics
- Scenario in orchard with the highest application rate of 3.040 kg a.s./ha

The PECsw seem to be very favourable (0.2-0.3 µg a.s./l after 7 days). Nevertheless, due to the very high aquatic toxicity of the a.s. and the fact that repeated applications are made, it is necessary that the notifier determines accurate short term and long term PEC in surface water in order to evaluate the chronic risk to aquatic organisms.

Table 2.8.2-1 : PEC_{sw} (mg a.s./l)

Time after applications (days)	Orchard (early growth stage) 3.040 kg a.s./ha			Orchard (late growth stage) 3.040 kg a.s./ha		
	direct application (drift = 100 %) (*)	application at 5 m of the water surface (drift = 20%)	application at 20 m of the water surface (drift = 4%)	direct application (drift = 100 %) (*)	application at 5 m of the water surface (drift = 10 %)	application at 20 m of the water surface (drift = 1.5%)
0	1.013	0.203	0.040	1.013	0.101	0.015
1	0.402	0.080	0.016	0.402	0.040	0.006
2	0.160	0.032	0.006	0.160	0.016	0.002
4	0.025	0.005	0.001	0.025	0.002	0.0004
7	0.002	0.0003	-	0.002	0.0002	-
14	-	-	-	-	-	-
21	-	-	-	-	-	-
28	-	-	-	-	-	-
42	-	-	-	-	-	-

- : < 0.0001 mg/l
(*) : unrealistic situation; only given to help the reader

PEC ground water :
The notifier should also provide information on the PEC groundwater.

2.8.3 Fate and behaviour in air

Not submitted. Information is required.

2.9 Effects on non-target species

2.9.1 Effects on terrestrial vertebrates

Toxicity to birds :
Acute toxicity and dietary toxicity studies were performed :
LD_{50} (*Colinus virginianus*)= 97 mg/kg bw
LC_{50} (*Anas platyrhynchos*) = 5200 mg/kg food
LC_{50} (*Colinus virginianus*) > 5200 mg/kg food

TER acute and short term for birds :
The risk assessment for birds is based on the following assumptions :
- Application in orchard of 3.04 kg a.s./ha (plums, peaches, cherries)
- Estimated initial residue in bird feed calculated in accordance with the method of Hoerger and Kenaga (1972)
- small birds (< 100 g bw) and large birds (> 100 g bw) scenarios were taken into account.

TER acute of 3 and 10 were calculated for small and large birds respectively. (Threshold value is 10)
TER short term of 55 were calculated for small and large birds (Threshold value is 10)

TER long term for birds:
TER long term were not calculated since no reproduction study was available. The evaluation of this risk is necessary :
- Indeed the effects on the reproduction at concentrations lower than the concentrations causing unpalatability of the food are not known.
- Continuous or repeated exposure is possible (4 to 6 applications made at 14 days interval in orchard)

<u>It is therefore necessary to evaluate the effects of ziram on the reproduction of birds and the long term risk to birds living in orchard.</u>

Seed treatment : No evaluation of the risks in the dossier.

TER acute and short term for small mammals :
The risk assessment for small mammals is based on the following assumptions :
- The following acute and short-term toxicity values were taken into account (LD_{50} rat = 267 mg/kg bw; NOAEL rat 28-90 days = 3 mg/kg food)
- Application in orchard of 3.04 kg a.s./ha (plums, peaches, cherries)
- Estimated initial residue in bird feed calculated in accordance with the method of Hoerger and Kenaga (1972)
- small mammals (< 100 g bw)

TER acute of 9.4 was calculated for small mammals. (Threshold value is 10)
TER short term of 0.03 was calculated for small mammals (Threshold value is 10)

Seed treatment : No evaluation of the risks in the dossier.

2.9.2 Effects on aquatic species

Toxicity to aquatic organisms :
The acute toxicity tests provided showed that ziram is very toxic to all groups of aquatic organisms :
LC_{50} (*Salmo gairdneri*, semi-static, 96h) = 1.7 mg a.s./l
LC_{50} (*Lepomis macrochirus*, continuous renewal, 96h) = 0.0097 mg a.s./l
EC_{50} (*Daphnia magna*, 48h) = 0.048 mg a.s./l
EC_{50} (*Selenastrum capricornutum*, 96 h) = 0.066 mg a.s./l

Chronic toxicity tests with fish, aquatic invertebrate and alga are necessary :
- The evaluation of the long term risk is impossible with the data already available.
- The EC_{50} for the three groups of organisms are < 0.1 mg a.s./l
- The risk due to repeated applications can not be excluded.

TER calculations :
The following assumptions were made to assess the risks for water organisms :
- application of 3.040 kg a.s./ha in orchard
- drift calculated according to Ganzelmeier (BBA)
- water depth = 30 cm

TER acute in the worst case situation (orchard - early growth stage - 5 or 20 m drift) are far below the threshold value of 100 for fish and aquatic invertebrates, of 10 for alga.

The evaluation of a long term risk (taking into account repeated applications) is impossible with the data available at this time.

Table 2.9.2-1 : TERacute for aquatic organisms exposed to ziram -Worst case scenario

Target crop	Distance (m)	Test species	Effect concentration	Estimated initial concentration (mg a.s./l)	TER
Orchard (early growth stage)	5	*Lepomis macrochirus*	0.0097 mg a.s./l	0.203	0.048
	20		0.0097 mg a.s./l	0.040	0.24
Orchard (early growth stage)	5	*Daphnia magna*	0.048 mg a.s./l	0.203	0.24
	20		0.048 mg a.s./l	0.040	1.2
Orchard (early growth stage)	5	*Selenastrum capricornutum*	0.066 mg a.s./l	0.203	0.32
	20		0.066 mg a.s./l	0.040	1.5

The notifiers must also address the following points : the bioaccumulation, the toxicity to sediment dwelling arthropods, the micro-mesocosm and the TER acute and long term.

2.9.3 Effects on bees and other arthropods

Bees :
Acute contact and oral toxicity tests were performed : LD_{50} > 100 µg a.s./ bee

The Qhc and Qho ratios were calculated taking into account the highest application rate in orchard (3040 g a.s./ha) Both ratios are 30.4 (< 50) indicating that the risk to bees is negligible.

Other non-target arthropods :
Two field tests were performed. They show that ziram is slightly harmful to harmful to a wide range of beneficial arthropods in situations close to actual use in orchard. The studies were not realized at the highest recommended rate of 3.040 kg a.s./ha.

No information on the soil dwelling arthropods was provided

2.9.4 Effects on earthworms and other soil macro-organisms

One acute toxicity study with *Eisenia foetida* was realized. (LC_{50} = 140 mg a.s./kg soil)

The following assumptions were made to assess the risks for earthworms :
- application rate of 3.040 kg a.s./ha in orchard
- 50 % of the deposit reaching the soil surface
- dispersion in a 5 cm soil layer

A TER acute of 69 was calculated (trigger value is 10) showing that the risk to earthworm is low. The evaluation of the risks resulting from repeated applications should be performed.

2.9.5 Effects on soil micro-organisms

The point must be addressed by the notifier.

2.9.6 Effects on other non-target organisms (flora and fauna)

No specific information was provided.

2.9.7 Effects on biological methods of sewage treatment

Not submitted. The point must be addressed by the notifier.

2.10 Classification and labelling

Current classification in annex I dir 67/548 /EEC : Muta cat 3 R40 Xn, R22 Xi, R36/37/38
At the pesticides meeting (Working group Classification and labelling of dangerous substances) Ispra, November 1995, it was decided to add **T^+ R26** to the present classification (waiting for a complete evaluation of the monograph).

Proposal by the notifier : Xn, N,R20/22, R36/37, R43, R50

Table 2.10-1 : Classification and labelling of ziram made by the Rapporteur

Classification :	**T+ , R26 : Xn, R22 : Xi, R41 : R43 : N, R50, R53**	
Labelling :		
Hazard symbol	**T+, N**	
Indication of danger:	**very toxic, dangerous for the environment**	
Risk phrases:	R22	harmful if swallowed
	R26	very toxic by inhalation
	R41	risk of serious damage to eyes
	R43	may cause sensitization by skin contact
	R50/53	very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Safety phrases:	S(2)	keep out of reach of the children
	S22	do not breathe dust
	S24	avoid contact with skin
	S26	in case of contact with eyes, rinse imediately with plenty of water and seek medical advice
	S37/39	wear suitable gloves and eye/face protection
	S45	in case of accident or if you feel unwell seek medical advice imediately
	S60	This material and its container must be disposed off as hazardous waste
	S61	Avoid release to the environment. Refer to special instructions safety data sheets

Table 2.10-2 : Justification for the proposal made by the Rapporteur concerning the classification and labelling of Ziram

Proposal	**Justification**
T+, R26	4h, inhalation study
Xn, R22	acute oral toxicity
Xi, R41	eye irritant in rabbit
R43	skin sensitizer
N, R50, R53	LC50 (*Lepomis macrochirus*) = 0.0097 mg a.s./l EC50 (*Daphnia magna*) = 0.048 mg a.s./l EC50 (*Selenastrum capricornutum*) = 0.066 mg a.s./l No indication on ready biodegradability of the a.s.

Table 2.10-3 : Classification and labelling of TRISCABOL 76 WG made by the Rapporteur

Classification:	**Xn, R 22 : Xi, R41**	
Labelling:		
Hazard symbol	**Xn**	
Indication of danger:	**Harmful**	
Risk phrases:	R22-41	
Safety phrases:	S2	keep out of reach of the children
	S13	keep away from food, drink and animal feedingstuffs
	S20/21	when using do not drink, eat or smoke
	S24	avoid contact with skin
	S26	in case of contact with eyes, rinse immediatly with plenty of water and seek medical advice
	S37/39	wear suitable gloves and eye/face protection
	S45	in case of accident or if you feel unwell, seek

LEVEL 3

Ziram

Proposed decision with respect to the application for inclusion of the active substance in Annex I

3.1 Background to the proposed decision

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3.2 Proposed decision concerning inclusion in Annex I

The following decision is proposed :

To remove from the market the plant protection products containing the a.s., with the possibility to reconsider the inclusion in annex I after submission of supplementary study results or additional information (Regulation 3600/92, article 7, 3 bis, point c)

3.3 Rational for the suspension of the decision to include the active substance in Annex I, or for the conditions and restrictions to be associated with a proposed inclusion in Annex I, as appropriate

The following reasons lead to the proposal for this decision :

Numerous studies, listed under Level 4 of this document, are required to perform a thorough evaluation of the active substance and to permit a decision to be made.

The information which was submitted by the notifiers was not sufficient to establish the minimal purity of the a.s. and the impurity profile unequivocally.
- An analysis of batches should be provided.
- The absence of impurities of toxicological significance (e.g. tetramethylthiourea) should be ascertained.

The information which was submitted by the notifiers was not sufficient to fully establish the absence of harmful effects on human health.
- The ADI was established on the basis of the LOAEL of the long-term toxicity study in rat (assessment factor : 1000)
- A valid metabolic pathway in mammals was lacking.
- The possible tumorigenic mechanism should be clarified.

The information which was submitted by the notifiers was not sufficient to fully establish that the residues do not have any harmful effects on the human health (risk for the consumer)
- It is very likely that extreme consumers of pome fruits would exceed the ADI.
- The plant and animal metabolism studies have failed to give information on the nature of intermediary degradation products to which the consumer could be exposed.
- Moreover there is no method of analysis for the selective determination of ziram.

The evaluation of the information which was submitted by the notifiers revealed that the fate and distribution in the environment was not fully addressed, that some non-target organisms are at risk : small mammals, aquatic organisms, non-target arthropods.
- Particularly in the case of aquatic organisms, the information available indicates an unacceptable risk.

LEVEL 4

Ziram

Further information to permit a decision to be made, or to support a review of the conditions and restrictions associated with the proposed inclusion in the Annex I

4.1 Identity of the active substance

Point addressed	Information or study required	Deadline
IIA 1.8	**Method of manufacture (Bakelite) :** **clarification of the manufacturing process with respect to the addition of additives**	
IIA 1.10	**Identity of impurities (Elf Atochem) (UCB) (FMC Foret) (Bakelite) :** **- *Elf Atochem* : complete description of additive and relevant impurities (e.g. tetramethylthiourea)** **- *UCB, Bakelite* : completed impurity profile of a.s. technical (mentioning <u>all</u> impurities (e.g. tetramethylthiourea) and additives) + all the necessary accompanying information regarding impurities and additives** **- *FMC Foret* : completed impurity profile of a.s. technical (mentioning <u>all</u> impurities (e.g. tetramethylthiourea)) + all the necessary accompanying information regarding impurities** **- *All notifiers* : information addressing the max. arsenic content, as stated in FAO-specification CP/82**	
IIA 1.11	**Analytical profile of batches (Elf Atochem) (UCB) (FMC Foret) (Bakelite) :** **- *All notifiers* : <u>complete</u> analytical profile (incl. a.s., <u>all</u> impurities and additives) + validation data for methods used (e.g. for determination of relevant impurities)**	
IIIA 1.4	**Composition of the formulations (UCB) :** **more detailed information on composition of ZIRAM 76 WG**	

4.2 Physical and chemical properties

4.2.1 Physical and chemical properties of the active substance

Point addressed	Information or study required	Deadline
IIA 2.1.1	**Study on melting point of purified a.s., according to EEC A1**	
IIA 2.2	**Study on relative density of purified a.s., according to EEC A3**	
IIA 2.3	**Full report on vapour pressure and volatility (Henry's law constant) of purified a.s.**	
IIA 2.4.1	**Description of physical state of purified a.s. and technical a.s., as well as information on colour of purified a.s.**	
IIA 2.4.2	**Information on odour of purified a.s.**	
IIA 2.5.1	**Full report on spectra (UV/VIS, NMR, MS, IR) of purified a.s., including molar extinction coefficients at relevant wavelengths and a table of signal characteristics for each spectrum**	
IIA 2.5.2	**Full report on spectra of impurities that are considered to be of toxicological significance (e.g. tetramethylthiourea)**	

Point addressed	Information or study required	Deadline
IIA 2.6	**Full report on solubility in water of purified a.s. according to EEC A6, including comment on effect of pH on solubility**	
IIA 2.7	**Full report on solubility in organic solvents of technical a.s.**	
IIA 2.8	**Full report on partition coefficient n-octanol/water of purified a.s.**	
IIA 2.9.3	**Study on quantum yield of direct phototransformation in water, including calculated theoretical lifetime in the top layer of aqueous systems and real lifetime of the a.s.**	
IIA 2.9.4	**Report on dissociation constant in water (pKa) of purified a.s.**	
IIA 2.10	**Estimation of photochemical oxidative degradation of a.s. (e.g. Atkinson method)**	
IIA 2.11.1	**Study on flammability of technical a.s., according to EEC A10**	
IIA 2.11.2	**Full report on autoflammability of technical a.s.**	
IIA 2.13	**Full report on explosive properties of technical a.s., according to EEC A14**	
IIA 2.14	**Study on surface tension of a.s., according to EEC A5**	
IIA 2.15	**Study on oxidizing properties of technical a.s., according to EEC A17**	

4.2.2 Physical and chemical properties of the plant protection product ZIRAM 76 WDG

Point addressed	Information or study required	Deadline
IIIA 2.2.1	**Study on explosive properties of ZIRAM 76 WDG, according to EEC A14**	
IIIA 2.2.2	**Study on oxidizing properties of ZIRAM 76 WDG, according to EEC A17**	
IIIA 2.3	**- Study on flammability of ZIRAM 76 WDG, according to EEC A10** **- Study on autoflammability of ZIRAM 76 WDG, according to EEC A16**	
IIIA 2.6.2	**"Definitive" study on bulk (tap) density of ZIRAM 76 WDG, according to CIPAC MT 169**	
IIIA 2.7.1	**Accelerated storage stability study according to CIPAC MT 46 (2 weeks at 54 °C), including determination of all relevant physico-chemical properties (a.s. content, pH, wet sieve residue, suspensibility and dispersibility)**	
IIIA 2.7.3	**Shelf-life study according to GIFAP n° 17 (ambient temperature, min. 2 years), including determination of relevant physico-chemical properties**	

Point addressed	Information or study required	Deadline
IIIA 2.8.1	**Report on wettability of ZIRAM 76 WDG, according to CIPAC MT 53.3.1**	
IIIA 2.8.2	**Study on persistent foaming of ZIRAM 76 WDG, according to CIPAC MT 47**	
IIIA 2.8.3	**- Full report on suspensibility of ZIRAM 76 WDG - Study on dispersibility of ZIRAM 76 WDG, according to CIPAC MT 174**	
IIIA 2.8.5	**Report on wet sieve residue of ZIRAM 76 WDG, according to CIPAC MT 167**	
IIIA 2.8.6.1	**"Definitive" study on nominal size range of ZIRAM 76 WDG granules, according to CIPAC MT 170**	
IIIA 2.8.6.2	**"Definitive" study on dust content of ZIRAM 76 WDG, according to CIPAC MT 171**	
IIIA 2.8.8.1	**Study on flowability of ZIRAM 76 WDG, according to CIPAC MT 172**	

4.3 Data on application and further information

Point addressed	Information or study required	Deadline
IIA 3.9	**Information on procedures for the decontamination of water in case of an accident**	

4.4 Methods of analysis

Point addressed	Information or study required	Deadline
IIA 4.1.2 IIIA 5.1.2	**Additional validation (e.g. accuracy) of the analytical methods for determination of relevant impurities in technical a.s. and WG formulations (see also IIA 1.11)**	
IIA 4.2.1 IIA 6.3 IIIA 5.2.1	**<u>Selective</u> method of analysis for determination of ziram in/on plant commodities**	
IIA 4.2.2 IIIA 5.2.2	**Validated analytical methods for determination of Ziram (and relevant metabolites) in soil**	
IIA 4.2.3 IIIA 5.2.3	**Additional validation of the analytical method for determination of Ziram in water (among other things, to ascertain if the LOQ for drinking water meets the EU drinking water limit of 0.1 µg/l)**	
IIA 4.2.4 IIIA 5.2.4 IIA 4.2.5	**Additional validation data (e.g. recovery at LOQ) regarding the method for determination of Ziram in air Additional validation data (e.g. fortification levels, RSD, LOQ)**	

Point addressed	Information or study required	Deadline
IIIA 5.2.5	regarding the method for determination of Ziram in body fluids and tissues	

4.5 Toxicology and metabolism

Point addressed	Information or study required	Deadline
IIA 5.1	Metabolism study in the rat	
IIA 5.4.1	Gene mutation test in mammalian cells	
IIA 5.5	Carcinogenicity : Explanation of ziram toxicity on thyroid and more particularly C-cells lesions should be provided.	
IIA 7.2	Worker exposure	

4.6 Residue data

Point addressed	Information or study required	Deadline
IIA 6.0	Storage stability of residue with fortification and storage of the whole fruit	
IIA 6.1	Metabolism in plants: nature of the intermediary degradation products in plants	
IIA 6.2	Metabolism in animals: nature of the intermediary degradation products in animals	
IIA 4.2.1 IIA 6.3	Selective method of analysis for determination of ziram in/on plant commodities	
IIA 6.5	Intended uses on pome fruits: proposal to reduce the exposure of extreme consumers to residues	
IIA 6.6	New supervised residue trials according to the intended uses with selective analysis of ziram or data sufficient to establish a conversion factor between total CS_2 residues and parent residues	
IIA 6.6	Further supervised residue trials according to the intended uses on almonds, apricots, plums and cherries	
IIA 6.7	Data to establish transfer factors from raw to processed commodities: - pome fruits: juice, pomace, sauce - cherries: preserves	

Point addressed	Information or study required	Deadline
	- plums: puree, prunes	

4.7 Environmental fate and behaviour

Point addressed	Information or study required	Deadline
IIA 7.1.1.2.1	Rate of degradation in three soils at 20°C Rate of degradation at 10°C	
IIA 7.1.1.2.2	Soil dissipation study (study ongoing)	
	Data on 1,1-dimethylurea (major metabolite of the aerobic soil study) physico-chemical characteristics, persistence, leaching potential, effect on human and non-target organisms	
IIIA 9.1.3	Calculation of PEC soil short-term and long term after repeated applications for the a.s. Calculation of PEC soil and groundwater for 1,1-dimethylurea	
IIA 7.1.2	Adsorption/desorption : stability of ziram in the test should be determined.	
IIA 7.1.3	Column leaching : Characterization of the radioactivity recovered in the leachate should be done.	
IIA 7.2.1.2	Photodegradates : Physico-chemical characteristics, persistence, effects on human and non-target organisms should be provided.	
IIA 7.2.1.3.1	Ready biodegradability of a.s.	
IIA 7.2.1.3.2	Water/sediment study with a.s.	
IIIA 9.2.1	PEC surface water, short term and long term, taking into account multiple applications in orchard.	
IIA 7.2.2	Fate and behaviour in air	

4.8 Ecotoxicology

Point addressed	Information or study required	Deadline
IIA 8.1.3	Subchronic and reproductive toxicity to birds	
IIIA 10.1	TER long term for birds (foliar spray in orchard) Evaluation of the risk to birds in case of seed treatment	
IIA 8.2.2	Chronic toxicity to fish	
IIA 8.23	Bioaccumulation potential in fish	
IIA 8.2.5	Chronic toxicity to aquatic invertebrates	
IIA 8.2.7	Effects on the organisms of the sediments	

Point addressed	Information or study required	Deadline
	Chronic toxicity to algae	
IIIA 10.2	**TER acute and long term for the aquatic organisms**	
IIIA 10.2.2	**microcosm or mesocosm study**	
IIA 8.3.2	**Effects on non-target arthropods - Soil dwelling arthropods**	
IIA 8.4.2	**Sublethal effects on earthworms**	
IIA 8.5	**Effects on soil non-target micro-organisms**	
IIIA 10.6	**Effects earthworms and other soil non-target macro-organisms**	
IIA 8.7	**Effects on biological methods of sewage treatment**	

4.9 Classification, packaging and labelling

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