Environmental Health Criteria 41

QUINTOZENE

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The **International Programme on Chemical Safety (IPCS)** is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

While every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication, mistakes might have occurred and are likely to occur in the future. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors found to the Manager of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

In addition, experts in any particular field dealt with in the criteria documents are kindly requested to make available to the WHO Secretariat any important published information that may have inadvertently been omitted and which may change the evaluation of health risks from exposure to the environmental agent under examination, so that the information may be considered in the event of updating and re-evaluation of the conclusions contained in the criteria documents.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Palais des Nations, 1211 Geneva 10, Switzerland (Telephone no. 988400 - 985850).

ENVIRONMENTAL HEALTH CRITERIA FOR QUINTOZENE

Following the recommendations of the United Nations Conference on the Human Environment held in Stockholm in 1972, and in response to a number of World Health Resolutions (WHA23.60, WHA24.47, WHA25.58, WHA26.68), and the recommendation of the Governing Council of the United Nations Environment Programme, (UNEP/GC/10, 3 July 1973), a programme on the integrated assessment of the health effects of environmental pollution was initiated in 1973. The programme, known as the WHO Environmental Health Criteria Programme, has been implemented with the support of the Environment Fund of the United Nations Environment Programme. In 1980, the Environmental Health Criteria Programme was incorporated into the International Programme on Chemical Safety (IPCS). The result of the Environmental Health Criteria Programme is a series of criteria documents.

A WHO Task Group on Environmental Health Criteria for Organochlorine Pesticides other than DDT (Endosulfan, Quintozene, Tecnazene, Tetradifon) was held at the Health Protection Branch, Department of National Health and Welfare Ottawa from 28 May - 1 June, 1984. The meeting was opened by Dr E. Somers, Director-General, Environmental Health Directorate, and Dr K.W. Jager welcomed the participants on behalf of the three co-sponsoring organizations of the IPCS (UNEP/ILO/WHO). The Task Group reviewed and revised the draft criteria document and made an evaluation of the health risks of exposure to quintozene.

The drafts of this document were prepared by Dr D.C. Villeneuve of Canada and Dr S. Dobson of the United Kingdom.

The efforts of all who helped in the preparation and finalization of the document are gratefully acknowledged.

* * *

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1. SUMMARY AND RECOMMENDATIONS

1.1 Summary

1.1.1 Identity, analytical methods, and sources of exposure

Technical quintozene (pentachloronitrobenzene) is a white solid with a musty odour, that, is used in formulation as a soil fungicide and as a seed dressing. Hexachlorobenzene is a possible major contaminant in technical quintozene.

Gas chromatography combined with electron capture detection is used for the analytical determination of quintozene.

Exposure of the general population is mainly via residues in the food.

1.1.2 Environmental concentrations and exposures

Quintozene persists in soil with a half-life of approximately 4 - 10 months. Part of it is lost from the soil by volatilization. Biodegradation, mainly to pentachloroaniline is an important route of conversion. Photodegradation is not important.

1.1.3 Kinetics and metabolism

There are large animal species differences in the absorption of quintozene from the gastrointestinal tract. There is no information on absorption via inhalation or via the skin. After ingestion, faecal elimination of unchanged material is an important route of excretion. Pentachloroaniline and mercapturic acid conjugates are the major metabolites found in urine. There is no tendency for bioaccumulation.

1.1.4 Studies on experimental animals

Quintozene is practically non-toxic according to the scale of Hodge & Sterner (1956). The oral LD_{50} for quintozene in the rat ranges from 1650 to more than 30 000 mg/kg body weight. WHO (1984) classified quintozene in the category of technical products unlikely to present an acute hazard in normal use.

In long-term studies, no-observed-adverse-effect levels are 1.25 mg/kg body weight and 0.75 mg/kg body weight for rats and dogs, respectively. At higher dosages, there is liver hypertrophy with some histopathological changes. In dogs, dose-related liver damage including fibrosis was induced.

Purified quintozene was not teratogenic at levels of up to 500 mg/kg body weight in mice. Positive results obtained with technical quintozene in mice (500 mg/kg body weight) implicate the involvement of hexachlorobenzene in the teratogenic response. Quintozene was not teratogenic in rats at levels up to 1563 mg/kg.

Quintozene is generally negative in short-term tests for genetic activity. In carcinogenicity studies where rats and mice were fed quintozene at levels up to 1200 mg/kg diet, equivocal or negative findings have been reported. Hexachlorobenzene, a possible impurity in technical quintozene, is carcinogenic to mice, rats, and hamsters.

1.1.5 Effects on man

Quintozene is a weak skin sensitizer, but not an irritant.

Except for 1 case of conjunctivitis in an occupational setting, instances of accidental overexposure have not been reported.

1.1.6 Effects on the environment

There are indications that quintozene applied at recommended rates as a soil fungicide could produce a significant adverse effect on earthworm survival. There is no evidence that quintozene represents a threat to other organisms tested. Its bioaccumulation in fish is low.

1.2 Recommendations

1. Further data on absorption resulting from different routes of exposure to quintozene are required.

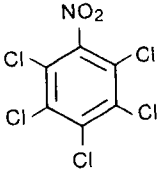
2. Levels of impurities, especially hexachlorobenzene, in quintozene should be kept to a minimum.

3. Adequate carcinogenicity studies are required on quintozene.

2. IDENTITY, PROPERTIES AND ANALYTICAL METHODS

2.1 Identity

Chemical structure:



Molecular formula: $C_6Cl_5NO_2$

CAS chemical name: pentachloronitrobenzene

Common trade names: avicol, botrilex, brassicol, earthcide, fartox, folosan, fomac 2, fungiclor, GC 3944-3-4, kobu, kobutol, KP 2, NCI-C00419, olpisan, PCNB, pentagen, terraclor, terrafum, tilcarex, tritisan. A complete list of trade names is available from IRPTC (1983).

CAS registry number: 82-68-8

Relative molecular mass: 295.36

2.2 Properties and Analytical Methods

2.2.1 Physical and chemical properties

Quintozene is a pale yellow-to-white (depending on the purity) solid with a musty odour and has a melting point of 142 - 146 °C. It is soluble in carbon disulfide, benzene, chloroform, ketones, and aromatic and chlorinated hydrocarbons but is practically insoluble in water (0.44 mg/litre at 20 °C); in ethanol its solubility is 2% at 25 °C (IARC, 1974). It has a vapour pressure at 20 °C of 10^{-8} •667 kPa (Berkowitz et al., 1976). Hexachlorobenzene is often found as a contaminant in quintozene and levels can range up to 3% (in the past, levels as high as 30% were found).

It is quite stable in soil but eventually degrades to pentachloroaniline (PCA).

Quintozene is primarily registered for use as a soil fungicide for use in agriculture and on field crops, selected vegetables, horticultural crops, and in greenhouses. It is also used as a seed-treatment fungicide for crop seeds such as

cotton, peanuts, soybeans, and grain. It has been formulated as wettable powder, dust, emulsifiable concentrate, granules, and combination products. It has been sold under a variety of trade names.

The first laboratory synthesis was reported in 1868 (Berkowitz et al., 1976). It was first introduced in Germany as a soil fungicide in the 1930s. It has been produced in the USA since 1962 (IARC, 1974).

Quintozene is produced by either the chlorination of nitrobenzene or the nitration of chlorinated benzenes. In 1972, production levels in the USA were estimated to be 1.3 million kg, of which 30 - 40% was exported (Berkowitz et al., 1976).

2.2.2 Analytical methods

Methods of cleanup and analysis for quintozene have been summarized by Berkowitz et al. (1976). These include a colorimetric and a gas chromatographic method. The latter is the most sensitive and can be used in combination with a microcoulometric (Burke & Holswade, 1964) or electron capture detector (Kuchar et al., 1969). Cleanup of extracts can be accomplished by column chromatography using silicic acid (Methratta et al., 1967) or florisil (US DHEW, 1973).

3. USES, ENVIRONMENTAL LEVELS AND EXPOSURES, TRANSPORT AND DISTRIBUTION

3.1 Uses

The major uses of quintozene are summarized in Table 1 and some information is provided on the quantities used.

Table 1. Usage data for quintozene in selected countries[a]

Area	Quantity	Year	Uses
Colombia	12 305 kg 15 926 kg 23 965 kg	1982 1981 1980	fungicide recommended for treatment of millet, corn, and sorghum
Malaysia			fungicide
Mexico	313 000 kg	1983	seed treatment
Sweden	10 000 kg 2000 kg	1981 1981	fungicide in various crops; Home and garden fungicide on lawns
Tanzania	500 tonne	1981-82	applied to bananas, cereals, beans, etc.
United Kingdom	22.89 tonne	1975-79	fungicide used on non-edible crops and turf; as a dust applied to soil before sowing or planting edible crops; used on onion seed; as a paste applied to the stems of cucumber plants
USA	2043 - 2183 tonne	1982	fungicide

[a] From: IRPTC, personal communication, 1984.

3.2 Levels and Exposures

General population

No data are available for the concentrations of quintozene in air or water.

It is persistant in soil, and is often present in crops grown on treated soil. In a market basket survey in the USA, residues ranged from 0.001 to 0.003 mg/kg in 6 out of 240 composites examined. Three of the composites contained only trace amounts. It was most common in the fats and oils class. Quintozene residues on lettuce in greenhouses sprayed at levels of 30 g/m^2 in the open air declined from 60 µg/g after 5 days to almost zero after 7 weeks (Dunsing & Windschild, 1976). In a study by Heikes (1980), it was found that residues in 11 samples of peanut butter averaged 5.05 µg/kg.

Infants and children

In a market basket survey by the US FDA (Johnson et al., 1979), quintozene was found in 2 out of 10 samples of food composites for infants 6-months-old, and one of these had only a trace amount. The residue values ranged from trace to 0.03 mg/kg. In the food composites for toddlers 2-years-old, PCNB was found in 4 out of 10 samples, 1 containing a trace amount, and the residues in the other sample ranging from 0.004 to 0.016 mg/kg. The residues occurred in the oils and fats class as in the adult survey.

PCNB does not appear to accumulate to any appreciable degree in cows' milk (Goursaud et al., 1972; Glofke, 1973).

3.3 Transport and Distribution

(a) Air

Contamination of the air is often due to volatilization from the soil. Quintozene has a relatively high volatility (10^{-6} •1775 kPa at 25 °C) and thus the principal mechanism of loss from the soil is volatilization (Lee, 1975). It has an affinity for the air-water interface and thus moist air passing over the soil could account for a percentage of the loss by a "codistillation" process. In a study done by Caseley, this amount was found to be 62% (Berkowitz et al., 1976). Such loss would be greater immediately after application and would depend on the adsorbent properties of the soil (Lee, 1975).

(b) Water

Since quintozene is practically insoluble in water, it may be assumed that leaching is negligible (Leistra & Smelt, 1974). However, few data are available on residues in water

bodies and drinking-water. In one study, urban storm run-off was analysed and quintozene was found in only negligible amounts or not at all. However, this has not been correlated with use patterns in the area (Dappen, 1974).

(c) Soil

The fate of quintozene in soil has been more extensively studied. It persists in Californian soils and has a half-life of 4.7 - 9.7 months (Wang & Broadbent, 1973). Longer half-lives were associated with soils rich in organic matter. In an analysis of 22 samples collected from potato fields, treated for 11 years, residues averaged 7.06 mg/kg with a range of 0.06 - 25.25 mg/kg (Beck & Hansen, 1974). In a study by Rautapaa et al. (1977), quintozene levels of 0.05 - 27.0 mg/kg were found in the soil of forest tree nurseries. In one case, it was found that all the quintozene applied (20 - 40 kg/ha) was left in the soil. No explanation was given for this phenomenon. The authors found that, in general, residues in cereal and clover fields were less than those in forest-tree nurseries. Residues in the soil of those cereal and clover fields were 0.4%. Appreciable levels of the associated impurities and metabolites were also found.

3.3.1 Abiotic degradation and bioccumulation

Studies on the photoreduction of quintozene have shown that ultraviolet irradiation results mainly in reductive dechlorination. Irradiation of solutions in hexane produces pentachlorobenzene, 1,2,4,5-tetrachlorobenzene, and 2,3,4,6- and 2,3,4,5-tetrachloronitrobenzene (Crosby & Hamadmad, 1971). However, this process is very slow and thus not likely to be important as a degradation route. Biologically, soil microorganisms convert quintozene to pentachloroaniline (PCA) and methylthiopentachlorobenzene (MTPCB) (Sijpensteijn et al., 1977).

Under aerobic growth conditions, fungi and actinomycetes have been shown to convert low concentrations of quintozene to PCA and MTPCB. In a related study, Ko & Farley (1969) observed that microorganisms converted quintozene to PCA and that this process was greatest in submerged soil. Although quintozene is taken up from the soil by plants, it does not accumulate to any important degree in animals (section 4.2)

4. KINETICS AND METABOLISM

4.1 Absorption

4.1.1 Inhalation

No information on the uptake of quintozene through inhalation is available.

4.1.2 Gastrointestinal tract

There are no studies investigating the absorption of quintozene from the gastrointestinal tract. However, studies relating to the faecal elimination of the parent material suggest that absorption by this route may be limited and species-dependent (section 4.4.2).

4.1.3 Dermal exposure

No information on the uptake of quintozene through dermal exposure is available.

4.2 Distribution and Storage

Human studies

No data are available to indicate the extent of storage and distribution of quintozene in man.

Animal studies

After feeding quintozene to dogs in the diet at levels of up to 1080 mg/kg, for 2 years, none was found in the kidney, brain, skeletal muscle, liver, spleen, fat, bile, blood, urine, and faeces (Borzelleca et al., 1971). Nor was quintozene detected in the skeletal muscle, liver, kidney, fat, or faeces of rats fed up to 500 mg/kg diet for 33 weeks (Borzelleca et al., 1971). Storage of quintozene did not occur in fat, skeletal muscle, liver, or kidney of cows administered an amount equivalent to 10 mg/kg diet for 12 weeks (Borzelleca et al., 1971). Only negligible amounts were detected in the milk of these cows. Borzelleca et al. (1971) did, however, find tissue storage of hexachlorobenzene and pentachlorobenzene, contaminants of technical quintozene, in rats, dogs, and cows in degrees paralleling their contents in the quintozene. After sheep were dosed orally with quintozene (31 - 32 mg/kg body weight), quintozene was detected in the

omental fat (0.5 mg/kg) for only 1 day (Avrahami & White, 1976). Sixteen weeks of feeding chickens a diet containing 300 mg quintozene/kg resulted in fat levels of 0.85 mg/kg and levels in the egg yolk of approximately 0.02 mg/kg (Simon et al., 1979). Quintozene was not detected in the bile, gall bladder, liver, blood, or muscle of these animals.

In another study where pregnant rats were administered quintozene at levels of 50 - 200 mg/kg body weight, from day 6 to 15 of gestation, residues were not detected in either maternal tissues (brain, liver, heart, spleen, kidney, adipose tissue) or in fetuses removed by Cesarean section (Villeneuve & Khera, 1975). In mice, 4 daily doses of 500 mg/kg body weight led to the appearance of the metabolites, pentachloroanisole and pentachlorophenyl sulfide in the fatty tissue of pregnant mice and fetuses; these results indicated placental transfer of the metabolites (Courtney et al., 1976).

Analyses of tissue from 2 Rhesus monkeys sacrificed 24 and 48 h after being administered 2 mg/kg body weight orally showed that quintozene was eliminated quickly and had virtually no tendency to accumulate (Koegel et al., 1979).

In another study, where Rhesus monkeys were fed a diet containing ^{14}C-quintozene at 2 mg/kg for 550 days, a storage curve was constructed by subtracting the excreted from the administered radioactivity. The storage curve reached a steady state plateau of 2 - 3% of the administered dose after 30 - 40 days of treatment (Muller et al., 1978).

4.3 Biotransformation

The proposed metabolic and excretory pathway for quintozene is shown in Fig. 1. In animals, the major biotransformation products that appear in urine are pentachloroaniline (PCA), formed by reduction of the nitro group, and mercapturic acids formed after replacement of the nitro group with glutathione and subsequent further metabolism. The relative contribution of each of these reactions to the overall biotransformation of quintozene is species dependent. Rabbits dosed orally with 2 g quintozene excreted 14% in the urine as N-acetyl-S-pentachlorophenylcysteine (PCC) and 12% as free and conjugated PCA. The balance of the dose was excreted unchanged in the faeces (Betts et al., 1955) (section 4.4.2). In rhesus monkeys and sheep, PCA was identified as the major metabolite (Avrahami & White, 1976; Muller et al., 1978), whereas, in the rat, PCC is the major metabolite (O'Grodnick et al., 1981).

In addition to the above primary metabolites, a number of minor metabolites have been identified. The nitro group can be replaced either with a methylthio group to form pentachlorothio-anisole (PCTA) or with a hydroxyl group to form

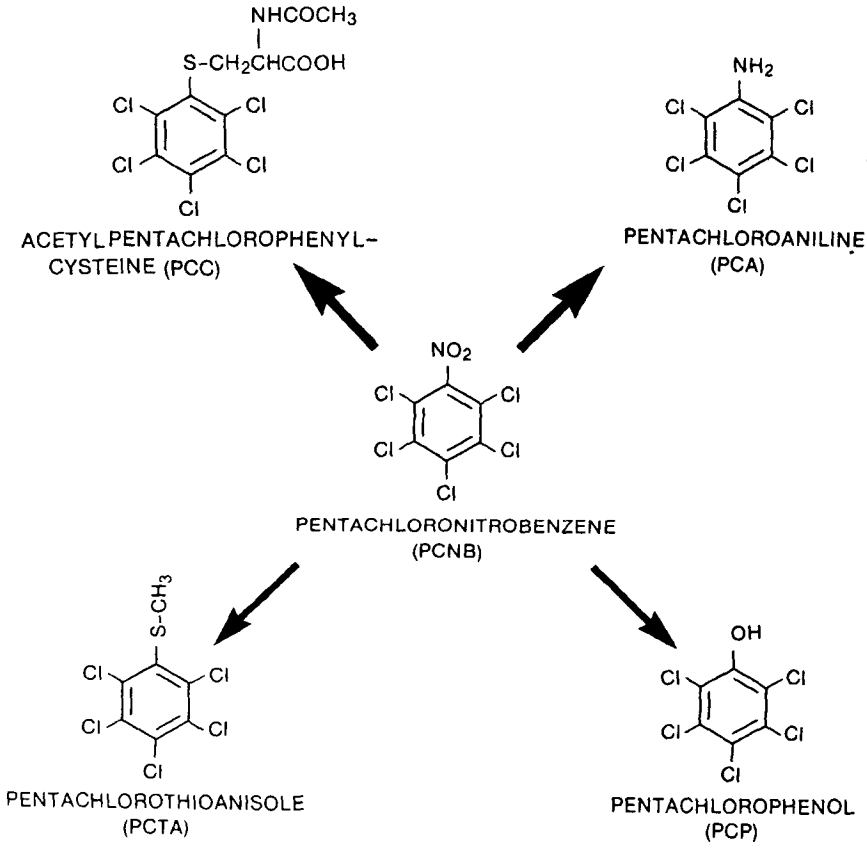


Fig. 1. Metabolic pathways of quintozene. In addition to the major biotransformations (broad arrows), an important route of excretion of orally-administered quintozene is as the unchanged compound in the faeces.

pentachlorophenol (PCP). PCTA has been shown to be formed in rats, dogs, chickens, and monkeys (Borzelleca et al., 1971; Muller et al., 1978; Dunn et al., 1979) and PCP in rabbits, rats, and monkeys (Betts et al., 1955; Muller et al., 1978; O'Grodnick et al., 1981). Following administration of quintozene pentachlorobenzene and tetrachloro-bis (methyl mercapto)-benzene were found in monkey urine (Muller et al., 1978) and pentachlorophenyl sulfide in rat urine (O'Grodnick et al., 1981).

Quintozene is converted by soil microorganisms and on plants to PCA and PCTA (Kuchar et al., 1969; Berkowitz et al., 1976; Sijpesteijn et al., 1977).

4.4 Elimination

4.4.1 Human studies

No information on the elimination of quintozene in man was found.

4.4.2 Animal studies

The major routes of elimination of ingested quintozene are via the faeces as unchanged material or in the urine as metabolites (Fig. 1)

The amount of quintozene eliminated unchanged in the faeces is species-dependent. Betts et al. (1955) administered 1,2, or 3 g of quintozene to rabbits by stomach tube and found an average of 46, 62, and 59% of the dose was eliminated unchanged in the faeces over 72 h. The faecal elimination was also variable (range 27 - 82% of the dose). In sheep dosed orally with 31 mg/kg body weight, approximately 80% of the dose was eliminated unchanged via the faeces (Avrahami & White, 1976). In metabolic studies carried out on Rhesus monkeys (Koegel et al., 1979), only 7.4% of the administered oral dose (2 mg/kg body weight) was excreted as quintozene in the faeces. After feeding rats with a diet containing 500 mg/kg diet, no detectable quintozene was found in the faeces, but unmetabolized quintozene was found in the faeces of dogs fed 1080 mg/kg diet for 2 years (Borzelleca et al., 1971).

Once absorbed, the elimination of quintozene is primarily as metabolites in the urine (section 4.3). Although quintozene has been found in bile, the relative importance of this finding for the elimination or enterohepatic circulation of quintozene is unknown. Nevertheless, it would appear that elimination by this route is species-dependent, since quintozene has been identified in the bile of monkeys (Kogel et al., 1979) and mice (Courtney et al., 1976) but not in the

bile of chickens (Kuchar et al., 1969; WHO 1975) or dogs (Borzelleca et al., 1971).

When a lactating cow was fed 5 mg/kg diet for 3 days, the parent compound was not detected in the milk using a method in which the sensitivity was 0.01 mg/kg (St. John et al., 1965). Traces of quintozene were found in milk from cows treated orally with the equivalent of 10 mg/kg diet for 8 weeks (Borzelleca et al., 1971). It was also found in the milk of untreated cows and analyses of the feed showed quintozene levels of 0.002 - 0.006 mg/kg.

Rhesus monkeys were fed diets containing quintozene at 2 mg/kg for 550 days. A storage curve was constructed by subtracting the excreted from the administered radioactivity. The storage curve levelled out after 30 - 40 days of treatment, resulting in a storage plateau of only 2 - 3% of the administered dose (Muller et al., 1978).

There was little accumulation of quintozene in fat tissue; slightly elevated concentrations are found in the liver and kidney as well as the thymus, lymph nodes, and bone marrow.

Residual levels in various tissues are given in Table 2.

Table 2. Tissue residue levels in Rhesus monkeys fed 2 mg/kg PCNB in the diet for 550 days[a]

Tissue	PCNB (mg/kg)	Tissue	PCNB (mg/kg)
Blood	0.07	adrenal cortex	0.08
Muscle	0.01	thymus	0.20
Brain	0.03	lymph nodes (large intestine)	0.12
Liver	0.19	bone marrow	0.13
Kidney	0.14	omental fat	0.21

[a] From: Muller et al. (1978).

As part of the same study, a Rhesus monkey dosed orally with radio-labelled quintozene at 2 mg/kg eliminated 92% of the radioactivity after 5 days, 91% of which was in the form of metabolites (Muller et al., 1978).

5. STUDIES ON EXPERIMENTAL ANIMALS

The toxicity and the residue data on quintozene have been reviewed several times by international bodies such as FAO/WHO (1970, 1974, 1976, 1978), IARC (1974), and CEC (1981). For their conclusion, refer to section 8. We refer to these reports, which contain more detailed information on the toxicity studies and residue data than the present report. Moreover, several unpublished studies have been evaluated and reported there.

5.1 Short-Term Studies

5.1.1 Single dose

Data on the acute toxicity of quintozene are summarized in Table 3.

Table 3. Acute toxicity of quintozene

Animal	Route	LD_{50} (mg/kg body weight)	References
rat (M)	oral	1710 (oil solution)	FAO/WHO (1970)
rat (F)	oral	1650 (oil solution)	FAO/WHO (1970)
rat	oral	> 30 000 (aqueous suspension)	FAO/WHO (1970)
rat	ip	5000 (aqueous suspension)	FAO/WHO (1970)
dog	oral	no deaths up to 2500 mg/kg	Berkowitz et al. (1976)
rabbit	dermal	no deaths up to 4000 mg/kg	Berkowitz et al. (1976)

Rabbits were dosed dermally once, with quintozene as a 30% solution in dimethyl phthalate at 2 dose levels (10 and 13.3 ml/kg) and observed for 14 days (Borzelleca et al., 1971). There was no evidence of toxicity or skin irritation.

Cats

Quintozene, dissolved in corn oil, administered orally to cats once at a level of 1600 mg/kg, caused a significant elevation in methaemoglobin levels and an approximately 8-fold increase in the number of erythrocytes containing Heinz bodies (Schumann & Borzelleca, 1978). This latter finding, together with the fact that a greater percentage of erythrocytes failed to stain properly in the course of time, suggested that a functional impairment of the erythrocyte had occurred.

5.1.2 Repeated dose

Rat

Five groups of 7 male and 7 female albino rats of weaning age were fed diets containing technical quintozene at 0, 63.5, 635, 1250, 2500, or 5000 mg/kg for 3 months. Growth and survival were adversely affected at 5000 mg/kg in both sexes and also in males at 2500 mg/kg. Liver hypertrophy was observed at all levels except in females fed 63.5 mg/kg. No haematological changes were seen and histological alterations were limited to fine vacuolization of liver cell cytoplasm at 5000 mg/kg (Finnegan et al., 1958). An unspecified number of young rats were fed diets containing 0 or 2000 mg quintozene/kg for 10 weeks (Wit et al., 1957). No gross effects other than decreased growth rate in the males were noted. Groups of 10 male and 10 female rats were fed diets containing 0, 1000, 5000, or 10 000 mg quintozene/kg for 90 days. The animals showed a slight growth depression at 5000 mg/kg and marked growth depression at 10 000 mg/kg (Hoechst, unpublished data, 1964).

Groups of 10 male and 10 female rats were fed diets containing technical quintozene at concentrations of 0, 25, 100, 300, 1000, or 2500 mg/kg diet for 2 years. No changes in blood haematology were found. In females, growth depression was observed at doses of 100 mg/kg diet and above (Finnegan et al., 1958).

Dogs

Groups of 3 mongrel dogs were fed diets containing 25, 200, or 1000 mg quintozene/kg for 1 year. No adverse effects were noted on body weight or survival. No haematological changes were seen and histopathological changes were restricted to liver cell enlargement, which was not dose-dependent (Finnegan et al., 1958). In a 2-year study, groups of 3 male and 3 female dogs were fed diets containing 0, 500, 1000, or 5000 mg quintozene/kg. Liver changes occurred in all groups in a dose-related manner. The 5000 mg/kg level produced severe liver damage including fibrosis, narrowing of hepatic cell cords, increased size of the periportal areas, and leukocyte infiltration. At 1000 and 500 mg/kg, the changes were similar but less pronounced. Reduced haematopoiesis and atrophy of bone marrow were observed in animals receiving the highest dose (FAO/WHO, 1970). Purebred beagles (4 per sex per dose) were fed diets containing quintozene at levels ranging from 5 to 1080 mg/kg for 2 years. Haematocrit values were depressed at 18 months in males receiving 30 and 180 mg/kg, but not in animals

receiving 1080 mg/kg. No dose-related effects were observed on urine analysis, blood chemistry, mortality, body weight, food consumption, or estrous cycle. Organ weight data revealed higher values for livers in dogs fed 1080 mg quintozene/kg. Histologically, dogs sacrificed at 2 years after receiving 180 or 1080 mg/kg showed hepatic and renal effects deemed reversible by the authors (Borzelleca et al., 1971).

Monkeys

Two male and two female rhesus monkeys were fed 2 mg quintozene/kg for 70 days. The haematological variables (haemoglobin, haematocrit, RBC, WBC), and the histopathological examination of the liver, stomach, small and large intestine, spleen, kidneys, heart, lung, thymus, cerebrum, cerebellum, pons, medulla, spinal cord, and bone marrow were carried out in 1 male and female monkey after 70 days. The histopathology, clinical chemistry, and serum cortisol levels remained within normal limits (Muller et al., 1978).

5.2 Reproduction Studies

Reproduction studies were carried out on rats fed a diet containing 0, 5, 50, or 500 mg quintozene/kg until the F/3b litters were weaned. Quintozene had no effect on fertility (pregnancies/mating), gestation (litters cast/pregnancies), viability (live at 4 days/live at birth), or lactation (weaned/live minus discards) indices. No dose-related histopathological abnormalities were recorded in any of the F_{3b} pups. It was not teratogenic to rats at dosages up to 1563 mg/kg body weight (Jordan & Borzelleca, 1973; Khera & Villeneuve, 1975; Courtney et al., 1976). Levels of 500 mg/kg body weight of technical quintozene (87% pure) administered from day 7 to 11 of gestation produced renal agenesis in C57Bl/6 mice, but none were produced with purified material (99%) (Courtney et al., 1976). Hexachlorobenzene, a major contaminant in the technical material, was implicated in the teratogenic response. Quintozene did not produce any teratogenic response in AKR mice when administered at levels up to 500 mg/kg diet (Berkowitz et al., 1976).

5.3 Mutagenicity

Quintozene was reported to give a positive mutagenic response in a host cell reactivation deficient strain of *E. coli* (Clarke, 1971). It was not mutagenic when studied in an Ames test system consisting of several bacterial strains using Aroclor 1254 activation (Mohn, 1971). It was reported to be

negative in a reverse mutation assay using 5 tester strains of Salmonella typhimurium and E. coli (Moriya et al., 1983). It was shown to be negative in a dominant lethal test in mice where the chemical was administered for 7 weeks in the diet (no concentrations specified) (Van Logten, 1977). It produced no significant increase in mutation rates in Salmonella typhimurium and Serratia marcescens; it also gave negative results in spot tests against the same strains of Salmonella typhimurium and Serratia marcescens (Buselmaier et al., 1973). Both FAO/WHO (1978) and CEC (1981) concluded that there were no indications for mutagenic activity.

5.4 Carcinogenicity

The carcinogenicity of quintozene was evaluated by IARC in 1973 (IARC, 1974). Studies evaluated at that time as well as additional studies are summarized below.

In a large screening study, 18 male and 18 female (C57BL/6 x C3H/Anf)F1 mice and similar numbers of (C57BL/6 x AKR)F1 mice were given single doses of 464 mg quintozene/kg body weight (unspecified purity) by stomach tube, when the animals were 7 days of age, and this same absolute dose was then given daily until the animals were 28 days of age. This was followed by a diet containing 1206 mg/kg diet, which was administered up to 78 weeks. Hepatomas were the only tumours found in excess over the controls; 2/18 male and 4/18 female (C57BL/6 x C3H/Anf)F1 mice developed hepatomas compared with 8/79 and 0/87 in controls. Of the (C57BL/6/ x AKR)F1 mice, 10/17 males and 1/17 females developed hepatomas compared with 5/90 and 1/82 in controls. The incidence of other tumours was similar in treated and control animals (Innes et al., 1969).

Ten stock albino mice of each sex were painted twice weekly with 0.2 ml of a 0.3% solution of quintozene in acetone for 12 weeks. This was followed by twice-weekly paintings with a 0.5% solution of croton-oil in acetone for 20 weeks followed by observation for 40 weeks. In a control group, acetone alone was given followed by treatment with croton oil. The total number of skin tumours at the end of croton-oil treatment was 12 in 9 surviving controls and 50 in 13 survivors in the quintozene group. One tumour in the quintozene group had progressed to a squamous-cell carcinoma. An infiltrating squamous-cell carcinoma was also observed in 1 control mouse killed 31 weeks from the start of the croton-oil treatment (Searle, 1966).

Two unpublished studies on the carcinogenicity of quintozene (containing 2.7% hexachlorobenzene) were reviewed by the FAO/WHO Joint Meeting on Pesticide Residues in 1975. Groups of 100 male and 100 female Swiss mice and 50 male and 50 female Wistar rats were administered levels of 0, 100, 400,

or 1200 mg/kg diet. In mice, a non-dose-related increase in the incidence of liver hyperplastic nodules was observed in males and an increased incidence of subcutaneous fibrosarcomas was observed in females at the highest dose level. No increased tumour incidence was reported in rats (FAO/WHO, 1976). No further details of this study are available.

Groups of 50 male and 50 females Osborne-Mendel rats and B6C3F1 mice were given technical grade quintozene (purity 97% with 12 impurities) in their diet for 78 weeks. In rats, the average dietary concentrations were 10 064 and 5417 mg/kg of diet for males and 14 635 and 7875 for females; in mice, average dietary concentrations were 5213 and 2606 for males and 8187 and 4093 for females. Observation continued for 33 - 35 additional weeks in rats and for 14 - 15 additional weeks in mice. Adequate numbers of animals survived long enough to permit the detection of late developing tumours. No statistically-significant increase in the incidence of neoplasms was seen in either species. It was concluded that quintozene was not carcinogenic under the conditions of this bioassay (NCI, 1978).

Hexachlorobenzene, a potential impurity in quintozene, is carcinogenic in mice, rats, and hamsters producing tumours of the liver (IARC, 1979; Smith & Cabral, 1980).

6. EFFECTS ON MAN

In patch tests, a quarter-inch square of cotton cloth was moistened with water, dipped in a 75% quintozene wettable powder (Olin formulation), and then placed on the volar surface of the right forearms of 50 human volunteers. The patches were then covered with a 1-inch square of aluminum foil held in place by a 2-inch square of adhesive tape. After 48 h, the patches were removed. No evidence of irritation was seen in any of the subjects. Two weeks later, the same test was repeated on the left arm of the same subjects. After 48 h, 46 of the 50 subjects showed no signs or irritation. In 3 of the 4 reported reactions, a 1-inch square area showed erythema, oedema, and small vesicle formation with marked itching; the 4th subject had only erythema and itching. Of the 46 subjects who were negative when the second patch was removed, 9 developed a delayed reaction. Time of onset varied from approximately 8 h to several days. In 2 of these persons, the reaction included erythema, oedema, small vesicle formation, and itching. The skin reaction reached a peak during the first few days of symptoms and subsided with time, with some scaling of the skin (Finnegan et al., 1958). One instance of keratoconjunctivitis has been reported in the literature (Fujita et al., 1976) and resulted from the application of the pesticide. Remission of the condition took a month.

7. EFFECTS ON THE ENVIRONMENT

7.1 Toxicity for Aquatic Organisms

Quintozene is of low toxicity for aquatic organisms. The only data on the toxicity of quintozene for aquatic organisms is from Nishiuchi & Yoshida (1972) who quote a 48-h LC_{50} value of 10 000 µg/litre for carp and a 3-h LC_{50} value for Daphnia of 40 000 µg/litre.

7.2 Toxicity for Terrestrial Organisms

7.2.1 Plants

Vishunavat & Shukla (1981) examined the effects of quintozene on seed germination, plant stand, and yield of lentils. There were no significant effects. Brown et al. (1982) did not find any effects on the germination of orchids when 99% pure quintozene was applied at concentrations of 25 and 50 mg/litre. At 100 mg/litre, Cattleya elongata did not germinate, but germination of Laelia was unaffected and Vanda tricolor showed improved germination. Quintozene eliminated growth of excised shoot tips in orchids of the Cymbidium family.

7.2.2 Earthworms

Roark & Dale (1979) reared earthworms Eisenia foetida in soil pre-mixed with quintozene at a dose of 0.679 g/4719 cm^3 of soil, corresponding to 226.8 g over 929 cm^2 of turf. The dose was calculated as the total of 3 applications of the recommended dosage for turf. The worms did not reproduce in treated soil. Survival of worms was not significantly reduced within the first 10 days, but fell to zero within 29 days of treatment with quintozene.

7.2.3 Bees

No information is available on toxicity of quintozene for bees. However, since the main uses of quintozene are on soil or as a seed dressing, it is unlikely that bees would be exposed.

7.2.4 Birds

Dunn et al. (1979a) fed white leghorns with concentrations of 0, 10, 50, 100, or 1000 mg quintozene/kg diet and examined egg production and hatchability. None of these concentrations

caused obvious toxic effects, death, or histopathological changes in either control or treated groups. Egg production during the 25th to the 35th week was not significantly affected. However, at a higher dose level of 1000 mg/kg diet, onset of egg production was delayed for 1 month, and the number of chicks hatched from fertile eggs significantly decreased from 91% in the controls to 69% in treated birds. Shell strength of the eggs was not significantly altered (Dunn et al., 1979a). In another study (Dunn et al., 1979b), the authors reported that bioaccumulation of PCNB or its metabolites only occurred in trace concentrations; body weight gains were significantly lower in hens fed 1000 mg quintozene/kg diet.

7.3 Toxicity for Microorganisms

Tu (1980) reported that quintozene at doses up to 5000 mg/litre did not induce any effects on 3 strains of the bacterium Rhizobium japonicum in culture. Quintozene also did not show any effects on 25 strains of Rhizobium bacteria, isolated from root nodules of red clover, at doses up to 1000 mg/litre in the culture medium (Heinonen-Tanski et al., 1982). Smiley & Craven (1979) applied quintozene 9 times annually for 3 years, at weekly intervals during July and August, to a turf of Kentucky blue grass. There were no significant effects on the populations of bacteria, actinomycetes, or fungi. The effects of quintozene on carbon dioxide evolution and on the enzyme activities in organisms in soil were observed by Mitterer et al. (1981). The recommended soil dosage of the fungicide caused an increase in carbon dioxide evolution from soil cultures. After a second and third application, this initial increase was followed by a decrease in carbon dioxide release to below the value for untreated control soil. Quintozene showed a severe and continuous inhibition of xylanase activity, in marked contrast to other fungicides tested.

7.4 Bioaccumulation and Biomagnification

Ogiso & Tanabe (1982) measured residues in different tissues of crop plants. High concentrations of quintozene in plant tissues relative to soil levels were only found in the outer layers of roots and tubers directly in contact with soil. There is little evidence of systemic uptake.

Kanazawa (1981) reported a bioconcentration factor for quintozene by top mouth gudgeon Pseudorasbora parva of 238. The flow-through system maintained water concentrations of between 5 and 20 µg quintozene/litre.

8. PREVIOUS EVALUATIONS OF QUINTOZENE BY INTERNATIONAL BODIES

The Joint Meeting on Pesticide Residues (JMPR) reviewed residues and toxicity data on quintozene in 1969, 1973, 1975, and 1977 (FAO/WHO, 1970, 1974, 1976, 1978). The conclusion in 1977 was that 25 mg/kg diet, equivalent to 1.25 mg/kg body weight was a no-observed-effect-level in the rat and 30 mg/kg diet, equivalent to 0.75 mg/kg body weight in the dog. On the basis of this, the estimate of an acceptable daily intake (ADI) for man was 0 - 0.007 mg/kg body weight.

IARC (1974) did not come to a conclusion on the carcinogenicity of quintozene because of lack of data at the time. FAO/WHO (1978) concluded that there were no indications that administration of quintozene resulted in carcinogenic activity.

CEC (1981) concluded that there was a need to set limits on the impurities present in technical quintozene.

WHO, in its "Guidelines to the Use of the WHO Recommended Classification of Pesticides by Hazard" (WHO, 1984), classified quintozene in the category of technical products unlikely to present an acute hazard in normal use.

Regulatory standards established by national bodies in 12 different countries (Argentina, Brazil, Czechoslovakia, the Federal Republic of Germany, India, Japan, Kenya, Mexico, Sweden, the United Kingdom, the USA, and the USSR) and the EEC can be found in the IRPTC (International Register of Potentially Toxic Chemicals) legal file (IRPTC, 1983).

9. EVALUATION OF HEALTH RISKS FOR MAN AND EFFECTS ON THE ENVIRONMENT

9.1 Evaluation of Health Risks for Man

Quintozene toxicity

Quintozene is practically non-toxic according to the scale of Hodge & Sterner (1956). The oral LD_{50} in rats was 1650 to more than 30 000 mg/kg body weight. WHO (1984) classified quintozene in the category of technical products unlikely to present an acute hazard in normal use.

No-observed-adverse-effect levels in long-term studies on the rat and the dog were 1.25 and 0.75 mg/kg body weight (25 and 30 mg/kg diet), respectively. In long-term studies with rats and at higher dosages (63 mg/kg diet), quintozene can give rise to liver hypertrophy with some histopathological changes and in dogs to more severe liver damage with fibrosis (5000 mg/kg diet). In short-term studies on female rats, quintozene caused induction of mixed-function oxidases.

Quintozene is both metabolised and excreted unchanged and does not accumulate in tissues.

Quintozene is not considered to be teratogenic.

Quintozene is generally negative in short-term tests for genetic activity. In carcinogenicity studies on rats and mice, equivocal or negative findings have been reported. Hexachlorobenzene, a possible impurity in technical quintozene is carcinogenic for mice, rats, and hamsters.

Except for 1 case of conjunctivitis in an occupational setting, no other cases of poisoning or adverse effects have been reported in man.

Exposure to quintozene

The general population can be exposed via residues in food, especially in oils and fats. Information on exposure from other sources is lacking. No cases of accidental or occupational overexposure have been reported.

Hazard assessment

With the exception of some data on residues in food, no human exposure data are available for quintozene. It is therefore difficult to evaluate the hazard for man of present exposure to this substance. Nevertheless, in view of its low toxicity in short-term and long-term animal studies, the data available on quintozene would indicate a low degree of concern in relation to human health effects.

9.2 Evaluation of Overall Environmental Effects

The only significant adverse effect reported for quintozene is on earthworms. According to laboratory tests, quintozene applied at recommended doses as a soil fungicide appears to have long-term toxic effects on the earthworm. Unfortunately, no observations of the effects on earthworms of quintozene alone, during field use, are available.

There is no evidence that quintozene represents a threat to non-target organisms. It has a very low acute toxicity for fish and Daphnia.

Its bioaccumulation by fish is low, and no effects have been reported on terrestrial plants, birds, or microorganisms.

9.3 Conclusions

1. The general population does not appear to be at risk from residues of quintozene in food.

2. Exposure of the general population via air and drinking-water could not be evaluated because of lack of data.

3. Occupational exposure has not been reported to cause any adverse effects.

4. There is limited information on the effects of quintozene in the general environment. It has been shown to be toxic to earthworms, in laboratory tests. Data on other organisms suggest that quintozene is not a problem in the general environment.

5. Quintozene does not biomagnify.

6. The major toxicological concern with quintozene is the presence of hexachlorobenzene as an impurity.

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