ZIRAM

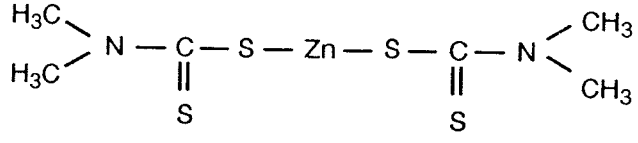
This substance was considered by a previous Working Group, in 1976 (IARC, 1976). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Synonyms, structural and molecular data*

Chem. Abstr. Serv. Reg. No.: 137-30-4
Replaced CAS Reg. Nos: 111922-61-3; 12768-61-5; 98391-07-2; 12773-04-5; 55870-88-7; 31300-71-7; 8059-74-3; 8070-07-3; 14459-91-7; 17125-91-6; 19488-81-4
Chem. Abstr. Name: (T-4)-Bis(dimethylcarbamodithioato-*S*,*S*′)-zinc
IUPAC Systematic Name: Zinc bis(dimethyldithiocarbamate)
Synonyms: Bis(dimethyldithiocarbamato)zinc; dimethylcarbamodithioic acid, zinc complex; dimethylcarbamodithioic acid, zinc salt; zinc, bis(dimethyldithiocarbamate); zinc dimethyldithiocarbamate



$C_6H_{12}N_2S_4Zn$ Mol. wt: 305.83

1.1.2 *Chemical and physical properties*

(*a*) *Description*: Crystalline white solid (Meister, 1990)
(*b*) *Melting-point*: 250°C (Budavari, 1989)
(*c*) *Density*: 1.66 at 25°C (Royal Society of Chemistry, 1989)
(*d*) *Spectroscopy data*: Infrared (prism [1296, 11231]; grating [15318] and nuclear magnetic resonance (proton [35587]) spectral data have been reported (US Environmental Protection Agency, 1975; Sadtler Research Laboratories, 1980, 1990).
(*e*) *Solubility*: Practically insoluble in water (65 mg/l); soluble at 25°C in ethanol (< 2 g/100 ml), acetone (< 0.5 g/100 ml), benzene (< 0.5 g/100 ml), carbon tetrachloride (< 0.2 g/100 ml) and dilute caustic solutions (Zweig, 1972; Budavari, 1989; Royal Society of Chemistry, 1989)

(*f*) *Vapour pressure*: Negligible at room temperature (Royal Society of Chemistry, 1989)
(*g*) *Stability*: Decomposed by acids and by ultraviolet irradiation; corrosive to iron and copper (Royal Society of Chemistry, 1989); hydrolysed slowly in water and stable in acidic media (Izmerov, 1982)
(*h*) *Conversion factor for airborne concentrations*[1]: $mg/m^3 = 12.51 \times ppm$

1.1.3 *Trade names, technical products and impurities*

Some common trade names are: Aaprotect; Aavolex; Aazira; Accelerator L; Aceto ZDED; Aceto ZDMD; Alcobam ZM; Carbazinc; Corozate; Crittam; Cuman; Cymate; Eptac 1; Fuclasin; Fuklasin; Hermat ZDM; Hexazir; Karbam White; Methasan; Methazate; Methyl zimate; Methyl zineb; Methyl Ziram; Mezene; Milbam; Molurame; Mycronil; Nocceler PZ; Orchard brand Ziram; Pomarzol Z-forte; Rhodiacid; Rodisan; Soxinal PZ; Soxinol PZ; Trikagol; Vancide; Vulcacure ZM; Vulkacite L; Z 75; Zarlate; Z-C Spray; Zerlate; Zirberk; Ziride; Zirthane.

Ziram is formulated in the USA as a wettable powder, a paste and as water-dispersible granules (Anon., 1989). In Europe, it is also formulated as a dustable powder, in liquid formulations and as suspension concentrates (Royal Society of Chemistry, 1986).

Ziram is combined in formulations with many fungicides and insecticides (Royal Society of Chemistry, 1989). A wettable powder is available in Europe that is a combination of ziram and copper(II) oxychloride. In the past, a product was available that contained ziram, methylarsinediyl bis(dimethyldithiocarbamate) and thiram (see monograph, p. 403) (Worthing & Walker, 1987).

1.1.4 *Analysis*

Selected methods for the analysis of ziram in various matrices are presented in Table 1.

1.2 Production and use

1.2.1 *Production*

Ziram was introduced around 1931 as a fungicide (WHO, 1988). It is prepared from zinc oxide, dimethylamine and carbon disulfide (Budavari, 1989).

Ziram is produced currently in Belgium, India, Italy, Spain and the USA (Meister, 1990). One company in the USA produced approximately 320 tonnes in 1989, 230 tonnes in 1985, 450 tonnes in 1980 and approximately 135 tonnes in 1975. In 1981, an estimated 350-400 tonnes of ziram were produced in the USA (Luttner, 1981). Ziram is produced in Spain for use in the rubber industry.

1.2.2 *Use*

Ziram has principal uses as an accelerator in the process of rubber vulcanization (Wolfe, 1971; see IARC, 1982) and as a protective foliar fungicide on fruit, nuts, vines, vegetables and ornamental plants. It is used extensively on almond and peaches to control shot hole, brown rot and peach leaf curl (Luttner, 1981). It is also used on pecans, apples and pears to control

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[1]Calculated from: mg/m^3 = (molecular weight/24.45) × ppm, assuming standard temperature (25°C) and pressure (760 mm Hg [101.3 kPa])

Table 1. Methods for the analysis of ziram

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Industrial and municipal wastewaters	Digest with acid to hydrolyse; trap evolved carbon disulfide in colour reagent; measure absorbance at 380 and 435 nm	Colorimetric	1.9 µg/l	Pressley & Longbottom (1982)
Specified crop samples	Decompose with the evolution of carbon disulfide, which is swept through a trap containing a solution of copper acetate and an amine to remove hydrogen sulfide; read absorbance of the coloured dithiocarbamate complex formed	Colorimetric	Not reported	US Food and Drug Administration (1989)
Specified crop samples and water	Extract with chloroform; evaporate; dissolve in methanol; add to mixture of methanolic 0.2% haematoxylin, aqueous 0.4% chloramine-T, and phosphate buffer solution at pH 7.0; heat; dilute with water; read absorbance at 555 nm	Spectrophotometric	Not reported	Sastry *et al.* (1988)
Formulations	Digest with acid; evolved carbon disulfide is trapped in methanolic potassium hydroxide; add phenolphthalein and starch indicator; titrate	Titrimetric	Not reported	Williams (1984)

scab and bull's-eye rot (Meister, 1990). The following amounts of ziram (active ingredient) were used in the USA in 1980 (tonnes): almonds, 320; peaches, 25-50; pears, 4-15; apricots, 5-10; and apples, 4-5. In the USA, ziram is registered for use as a fungicide in the following industrial applications: cooling-water slime control, paper-mill slime control, provision of mould resistance to paper and paperboard, and preservation of adhesives, textiles, paper coatings and industrial yarn and fabrics (Luttner, 1981). It is used as a wildlife repellant, when smeared as a paste onto tree trunks or sprayed onto ornamental plants, dormant fruit trees and other crops (Royal Society of Chemistry, 1989). In the USSR, ziram is used on potatoes for combatting phytophthora infection; other agricultural uses are prohibited. It is also used as a curing agent in the rubber industry (Izmerov, 1982).

1.3 Occurrence

1.3.1 *Water*

When precipitated to the bottom of bodies of water, thiram persisted for months. During cooking, ziram decomposed to thiram, tetramethylthiourea and dimethylamine dimethyldithiocarbamate (Izmerov, 1982).

1.3.2 *Food*

In the USSR, within two to five weeks after spraying with a 0.8-2.0% suspension of ziram, residual amounts in grapes and tomatoes were 0.1-0.8 mg/kg. Peelings of unwashed

apples contained 1.0 mg/kg, and pulp of washed apples contained 0.04 mg/kg of ziram. The degradation products of ziram (thiram, dimethylamine dimethyldithiocarbamate and sulfur) were detected in fruit in the USSR two to three months after treatment (Izmerov, 1982).

1.4 Regulations and guidelines

The USSR has established a MAC in industrial air of 0.05 mg/m^3 and a recommended maximum concentration of 0.01 mg/l in water reservoirs used as sources for drinking-water (Izmerov, 1982).

National pesticide residue limits for ziram in foods are presented in Table 2 and Codex maximum residue limits in Table 3.

Table 2. National pesticide residue limits for ziram in foods[a]

Country	Residue limit (mg/kg)	Commodities
Australia	7	Fruit, vegetables
Austria	25[b]	Hops
	2[b]	Fruit, vegetables
	0.05[b]	Other
Belgium	2[c]	Fruit, other vegetables
	0.5[c]	Bulb vegetables, grains
	0.2[c,d]	Potatoes
	0[c,e] (0.02)	Other
Brazil	7[f]	Citrus fruit, broccoli, kale, cabbage, squash, watermelons, peanuts
	5[f]	Grapes
	3[f]	Apples, peaches, pears, strawberries, tomatoes, figs, guava, papaya, coffee
	1.0[f]	Honeydew melon
	0.5[f]	Cucumbers
	0.2[f]	Wheat, rice, cashew nuts, kaki
	0.1[f]	Potatoes
Canada	7[g]	Apples, apricots, beans, beetroot, blackberries, black-eyed peas, blueberries (huckleberries), broccoli, Brussels' sprouts, cabbage, carrots, cauliflower, celery, cherries, collards, cranberries, cucumbers, eggplants, gooseberries, grapes, kale, kohlrabi, lettuce, loganberries, melons, onions, peaches, peanuts, pears, peas, peppers, pumpkins, quinces, radishes, raspberries, rutabagas, spinach, squash, strawberries, summer squash, tomatoes, turnips
Chile	5[b]	Grapes
	3[b]	Apples, peaches, pears, tomatoes
	1.0[b]	Lettuce, cherries, plums
	0.5[b]	Carrots
	0.2[b]	Wheat
	0.1[b]	Potatoes
Finland	1.0[b]	Others (except cereal grains)
	0.5[b]	Carrots
	0.1[b]	Bananas, potatoes

Table 2 (contd)

Country	Residue limit (mg/kg)	Commodities
Germany	25[b]	Hops
	2[b]	Vegetables (except cucumbers, tomatoes), fruit, spices, raw coffee, tea, tea-like products, oilseed
	1.0[b]	Cucumbers, tomatoes
	0.2[b]	Other vegetable foodstuffs
Israel	5[b]	Celery, currants (black, red), grapes
	3[b]	Apples, peaches, pears, strawberries, tomatoes
	1.0[b]	Bananas (whole), cherries, plums
	0.5[b]	Endives, lettuce, melons
	0.2[b]	Beans (in pods), carrots, cucumber
	0.1[b]	Wheat, banana pulp, potatoes
Italy	2[h]	Fruit, garden vegetables, cereals
	0.2[h]	Other products intended for food use
Japan	1.0	Persimmon, pear, peach, apple
Kenya	7	Apples, apricots, beans, beetroot, blackberries, blueberries, boysenberries, broccoli, Brussels' sprouts, cabbage, carrots, cauliflower, celery, cherries, collards, cranberries, cucumbers, dewberries, eggplants, gooseberries, grapes, kale, kohlrabi, lettuce, loganberries, melons, nectarines, onions, peaches, peanuts, pears, peas, peppers, pumpkins, quinces, radishes, raspberries, rutabagas, spinach, squash, strawberries, summer squash, tomatoes, turnips, youngberries
	0.1	Almonds
Netherlands	4[c]	Lettuce
	3[c]	Berries, small fruit
	2[c]	Other fruit, other vegetables
	1.0[c]	Cucumbers, melons
	0.5[c]	Bulb vegetables, cereals
	0.2[c,i]	Pulses, potatoes
	0[c,e] (0.2)	Other
Singapore	5	Fruit, grains, vegetables
Spain	4[b]	Grapes, hops, strawberries
	3[b]	Other fruit and vegetables (except potatoes)
	0.2[b]	Potatoes and other plant products
Sweden	1.0[b]	Fruit and vegetables
	0.5[b]	Carrots
	0.1[b,d]	Potatoes, cereals and hulled grain, flakes and flour made from cereal
Switzerland	50[b]	Tobacco
	2[b]	Fruit, vegetables (except potatoes), lettuce
	0.5[b]	Bananas (pulp)
	0.1[b]	Cereals
	0.05[b]	Potatoes

Table 2 (contd)

Country	Residue limit (mg/kg)	Commodities
USA	7[g]	Apples, apricots, beans, beetroot (with or without tops) or beetroot greens alone, blackberries, blueberries (huckleberries), boysenberries, broccoli, Brussels sprouts, cabbage, carrots, cauliflower, celery, cherries, collards, cranberries, cucumbers, dewberries, eggplants, gooseberries, grapes, kale, kohlrabi, lettuce, loganberries, melons, nectarines, onions, peaches, peanuts, pears, peas, peppers, pumpkins, quinces, radishes (with or without tops) or radish tops, raspberries, rutabagas (with or without tops) or rutabaga tops, spinach, squash, strawberries, summer squash, tomatoes, turnips (with or without tops) or turnip greens, youngberries
	0.1[g]	Almonds, pecans
USSR[j]	0.03	Foodstuffs
Yugoslavia	2[c]	Fruit, vegetables, tobacco
	0.05[c]	Other food commodities

[a]From Health and Welfare Canada (1990)
[b]Dithiocarbamates determined and expressed as carbon disulfide
[c]As dithiocarbamates
[d]The figure in parentheses is the lower limit for determining residues in the corresponding product according to the standard method of analysis.
[e]Residues shall be absent; the value in parentheses is the highest concentration at which this requirement is still deemed to have been met.
[f]Provisional tolerance
[g]Calculated as zineb
[h]Residues expressed as carbon sulfide; alone or combined with dithiocarbamates
[i]A pesticide may be used on an eating or drinking ware or raw material without a demonstrable residue remaining behind. The value listed is considered the highest concentration at which this requirement is deemed to have been met.
[j]From Izmerov (1982)

Table 3. Codex maximum residue limits for ziram[a]

Commodity	Maximum residue limit[b] (mg/kg)
Apples	3
Bananas	1
Carrots	0.5
Celery	5
Cherries	1
Common beans	0.5
Cucumbers	0.5
Currants (black, red, white)	5
Endives	1
Grapes	5
Lettuce, head	5

Table 3 (contd)

Commodity	Maximum residue limit[b] (mg/kg)
Melons, except watermelon	1
Peaches	3
Pears	3
Plums (including prunes)	1
Potatoes	0.1
Strawberries	3
Tomatoes	3
Wheat	0.2

[a]From Codex Committee on Pesticide Residues (1990); as dimethyl dithiocarbamates resulting from use of ferbam or ziram
[b]Determined and expressed as mg/kg carbon disulfide. The Joint Meeting on Pesticide Residues of 1980 (FAO/WHO, 1981) required further information on use patterns and data from residue trials before its estimates could be confirmed; as these requirements have not been met, the proposed limits, except that for lettuce (head), should be regarded as temporary. The proposal for lettuce (head) was made in 1985 without a requirement for further work or information.

Ziram was evaluated at the joint meetings of the FAO/WHO Expert Committee on Pesticide Residues in 1965, 1967, 1974, 1977 and 1980 (FAO/WHO, 1965, 1968, 1975, 1978, 1981). In 1977, the Committee established an acceptable daily intake for humans of 0.02 mg/kg bw (FAO/WHO, 1978), which was confirmed in 1980 for ziram and for the sum of ferbam and ziram (FAO/WHO, 1981; Codex Committee on Pesticide Residues, 1990).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Several studies on the carcinogenicity of ziram were summarized in a previous monograph (IARC, 1976), but, because of deficiencies in various aspects of study design, performance and/or reporting, the present Working Group did not consider them further. The studies in question are those of Hodge *et al.* (1956), the US National Technical Information Service (1968), Chernov and Khitsenko (1969) and Andrianova and Alekseev (1970).

Oral administration

Mouse: Groups of 49-50 male and 50 female B6C3F$_1$ mice, six weeks of age, were fed diets containing 600 or 1200 mg/kg ziram (89% pure, with 6.5% thiram, 2% other zinc salts and 2% unidentified impurity) for 103 weeks; survivors were killed one to three weeks later.

A group of 50 males and 50 females served as untreated controls. Survival was comparable in the treated and control groups. The incidence of lesions described by the authors as alveolar/bronchiolar adenomas was significantly ($p < 0.05$, trend) increased in female mice: control, 2/50; low-dose, 5/49; and high-dose, 10/50 ($p < 0.05$). The incidence of alveolar/bronchiolar carcinomas in female mice was: control, 2/50; low-dose, 1/49; and high-dose, 1/50. No increase in the incidence of tumours at any site was observed in males (US National Toxicology Program, 1983).

Rat: Groups of 50 male and 50 female Fischer 344/N rats, five weeks old, were fed diets containing 300 or 600 mg/kg commercial-grade ziram (89% pure, with 6.5% thiram, 2% other zinc salts and 2% unidentified impurity) for 103 weeks; survivors were killed one to four weeks later. A group of 50 males and 50 females served as untreated controls. Survival at the end of the experiment was: males—control, 33/50; low-dose, 34/50; and high-dose, 40/50; females—control, 37/50; low-dose, 44/50; and high-dose, 46/50. The incidence of C-cell carcinomas of the thyroid was significantly higher in high-dose males ($p < 0.05$) than in controls, with a significant positive trend (controls, 0/50; low-dose, 2/49; and high-dose, 7/49; $p < 0.01$). The combined incidence of C-cell adenomas and carcinomas in male rats also showed a significant positive trend (control, 4/50; low-dose, 9/49; and high-dose, 12/49; $p < 0.05$). No increase was observed in the incidence of tumours at any other site in males or in females (US National Toxicology Program, 1983).

4. Other Relevant Data

The toxicology of dithiocarbamates has been reviewed (WHO, 1988).

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

Water-soluble metabolites were found in the blood, kidneys, liver, ovaries, spleen and thyroid of female rats 24 h after oral administration of radiolabelled ziram; unchanged ziram was excreted in the faeces (Izmirova, 1972; Izmirova & Marinov, 1972).

Administration of ziram with nitrite in aqueous solution by stomach tube to rats led to the formation of detectable amounts of *N*-nitrosodimethylamine in the stomach contents after 15 min (Eisenbrand *et al.*, 1974).

4.2 Toxic effects

4.2.1 *Humans*

Ingestion of 0.5 litre of a solution of ziram of unknown concentration was fatal within a few hours; nonspecific pathology was observed (Buklan, 1974). A case of contact dermatitis has also been reported (Manuzzi *et al.*, 1988).

4.2.2 *Experimental systems*

The oral LD_{50} of ziram in rats was 1400 mg/kg bw, and lethal oral doses in guinea-pigs and rabbits were in the range 100-150 and 100-1020 mg/kg bw, respectively. The

intraperitoneal LD_{50} in rats was 23-33 mg/kg bw, and lethal intraperitoneal doses in guinea-pigs and rabbits were in the range 20-30 and 5-50 mg/kg bw, respectively. A dog tolerated doses of 25 mg/kg bw per day for one month (Hodge *et al.*, 1952); convulsions occurred in animals given this dose daily for one year (Hodge *et al.*, 1956).

A glycogenolytic response was elicited in rats after an intraperitoneal injection of 10 mg/kg bw ziram (Dailey *et al.*, 1969). Like most dithiocarbamates, ziram induces the accumulation of acetaldehyde in the blood of rats administered ethanol concurrently (van Logten, 1972).

In a 24-month chronic feeding study in rats, epiphyseal abnormalities in the long bones of the hind legs were observed in males and females at the highest dose tested (2000 ppm [mg/kg] in the diet; Enomoto *et al.*, 1989).

Ziram was reported to inhibit epoxide hydrolase and glutathione *S*-transferase in rat liver both *in vivo* and *in vitro* (Schreiner & Freundt, 1986).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

Administration of ziram at 50 or 100 mg/kg bw per day by gastric intubation to CD rats during the first five days of pregnancy reduced fetal weight by day 21 of gestation. Treatment at 25 mg/kg bw per day and above on days 6-15 resulted in embryotoxicity in the presence of maternal toxicity; at 100 mg/kg bw, a slight increase in the incidence of visceral malformations was observed (Giavini *et al.*, 1983).

Injection of ziram into the air chamber of eggs prior to incubation was embryolethal to chicks (LD_{50}; 2.1 μg/egg) (Gebhardt & van Logten, 1968).

4.4 Genetic and related effects (see also Table 4 and Appendices 1 and 2)

4.4.1 *Humans*

Peripheral blood lymphocytes from four male and five female workers who handled and packaged ziram were analysed for chromosomal aberrations. Average concentrations of ziram dust in the air of the work place were estimated to be 1.95 mg/m^3 in the store and 3.7 mg/m^3 in the packing area, but some were up to 71.3 mg/m^3. Despite protective measures (respirators and rubber gloves), ziram was detected on the skin of the workers' hands at concentrations of approximately 0.02 mg/m^2. Four controls (three women and one man) were matched with respect to age and residence. A marked increase in chromatid- and chromosome-type aberrations was observed in the exposed people as compared to the controls. The increase was about six-fold, and the exposed person in each pair had a significantly increased aberration frequency over the mean control level (Pilinskaya, 1970). [The Working Group noted the small number of individuals investigated in this study.]

4.4.2 *Experimental systems*

Ziram caused DNA damage and point mutation in bacteria, and these effects were increased by the presence of exogenous metabolic systems. It induced neither gene

Table 4. Genetic and related effects of ziram

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
BSD, *Bacillus subtilis rec* strain, differential toxicity	+	0	0.6000	Shirasu *et al.* (1976)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	2.5000	Hedenstedt *et al.* (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	+[c]	30.0000	Wildeman & Nazar (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	17.0000	Haworth *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	15.0000	Moriya *et al.* (1983)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	(+)	20.0000	Brooks *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	5.0000	Hedenstedt *et al.* (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	10.0000	Brooks *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	(+)	50.0000	Haworth *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	-	2500.0000	Moriya *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	0	50.0000	Hedenstedt *et al.* (1979)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	+	+	40.0000	Brooks *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	(+)	(+)	50.0000	Haworth *et al.* (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	2500.0000	Moriya *et al.* (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	-	0	50.0000	Hedenstedt *et al.* (1979)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	-	-	80.0000	Brooks *et al.* (1983)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	-	-	2500.0000	Moriya *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	50.0000	Hedenstedt *et al.* (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	(+)	30.0000	Wildeman & Nazar (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	-	10.0000	Brooks *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	(+)	50.0000	Haworth *et al.* (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	2500.0000	Moriya *et al.* (1983)
EC2, *Escherichia coli* WP2 *hcr*, reverse mutation	-	-	2500.0000	Moriya *et al.* (1983)
SCG, *Saccharomyces cerevisiae*, mitotic gene conversion	-	0	1000.0000	Siebert *et al.* (1970)
HSC, *Hordeum vulgare* (barley), chromosomal aberrations	-	0	500.0000	George *et al.* (1970)
DMM, *Drosophila melanogaster*, somatic mutation	+	0	130.0000 larval feeding	Tripathy *et al.* (1989)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	-	0	50.0000 adult injection	Benes & Sram (1969)

Table 4 (contd)

Test system	Result[a]		Dose[b] LED/HID	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	+	0	500.0000 adult feeding	Donner *et al.* (1983)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	+	0	54.0000 larval feeding[d]	Hemavathy & Krishnamurthy (1989)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	+	0	130.0000 larval feeding	Tripathy *et al.* (1989)
DMH, *Drosophila melanogaster*, translocation	-	0	162.0000 larval feeding[d]	Hemavathy & Krishnamurthy (1989)
* *Drosophila melanogaster*, germ-cell mutation	+	0	130.0000 larval feeding	Tripathy *et al.* (1989)
G9H, Gene mutation, Chinese hamster lung V79 cells *in vitro*, *hprt* locus	-	-	0.0800	Donner *et al.* (1983)
G5T, Gene mutation, mouse lymphoma L5178Y cells *in vitro*, *tk* locus	+	0	0.1000	McGregor *et al.* (1988)
SIC, Sister chromatid exchange, Chinese hamster CHO cells *in vitro*	-	-	1.7500	Gulati *et al.* (1989)
CIC, Chromosomal aberrations, Chinese hamster CHO cells *in vitro*	+	+	0.0250	Gulati *et al.* (1989)
TCL, Cell transformation, BHK hamster cells	0	-	0.0500	Brooks *et al.* (1983)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	0	0.0030	Pilinskaya (1971)
MVM, Micronucleus test, Swiss mouse bone marrow *in vivo*	+	0	95.0000 × 2 po[d]	Hemavathy & Krishnamurthy (1988)
CGC, Chromosomal aberrations, germ cells, Swiss mouse	+	0	95.0000 × 5 po[d]	Hemavathy & Krishnamurthy (1988)
DLM, Dominant lethal test, C3H mouse	(+)	0	2.0000 × 21 po	Cilievici *et al.* (1983)
DLM, Dominant lethal test, AK mouse	(+)	0	2.0000 × 21 po	Cilievici *et al.* (1983)
CVH, Chromosomal aberrations, human lymphocytes *in vivo*	+	0	0.0000	Pilinskaya (1970)

*Not displayed on profile

[a] +, positive; (+), weakly positive; -, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)

[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw

[c] Positive with plant activation system also

[d] Cuman L (27% ziram) was tested; dose represents ziram concentration

conversion in yeast nor chromosomal aberrations in *Hordeum vulgare*. In *Drosophila melanogaster*, ziram induced gene mutation in feeding studies but not when given by injection; it did not induce chromosomal translocation. Gene mutation was induced in mouse lymphoma L5178Y cells at the *tk* locus but not in Chinese hamster V79 cells at the *hprt* locus. [The Working Group noted that this discrepancy may be due to the different concentrations used and the difference in sensitivity of these two tests.] Chromosomal aberrations were induced in cultured rodent and human cells, whereas there was no induction of either sister chromatid exchange or anchorage-independent growth in rodent cells (Brooks *et al.*, 1983).

In vivo, ziram induced micronuclei in mouse bone marrow and chromosomal aberrations in mouse spermatogonia. Weak activity was reported in tests for dominant lethal mutation in male mice. [The Working Group noted the very low doses given in the latter tests.]

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Ziram is used primarily as a rubber vulcanization accelerator but is also used as a foliar fungicide, mainly on fruit and nuts. It has been in commercial use since the 1930s.

Ziram has been formulated for use as a wettable powder, a paste and water-dispersible granules and also in combination with other pesticides.

Exposure can occur during its production, its use in the rubber industry and its application as a fungicide, and, at much lower levels, from consumption of foods containing residues.

5.2 Carcinogenicity in humans

No data were available in the Working Group.

5.3 Carcinogenicity in experimental animals

Ziram was tested adequately for carcinogenicity by oral administration in one study in mice and one study in rats. In mice, the incidence of benign lung tumours was increased in females. In rats, a dose-related increase in the incidence of C-cell thyroid carcinomas was observed in males.

5.4 Other relevant data

In single studies, ziram caused embryotoxicity and minor malformations in rats and embryolethality in chicks hatched from injected ova.

An increased frequency of chromatid and chromosomal aberrations was seen in peripheral blood lymphocytes of workers who handled and packaged ziram.

Ziram was clastogenic in mammalian cells *in vivo* and *in vitro* and induced mutations in cultured rodent cells and in insects and bacteria.

5.5 Evaluation[1]

No data were available from studies in humans.

There is *limited evidence* in experimental animals for the carcinogenicity of ziram.

Overall evaluation

Ziram *is not classifiable as to its carcinogenicity to humans (Group 3).*

6. References

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[1]For definition of the italicized terms, see Preamble, pp. 26-28.

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