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Technical Information

Summary of Toxicity Data on Methyl Isothiocyanate (MITC)

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OUTLINE OF THE PRODUCTS
(Di-trapex and Trapexide)

It is well known that MITC vapourizes and diffuses through the soil immediately after injection into the soil and controls soil fungi, soil insects and nematodes, and is also effective against weed seeds, whilst 1,3-D (1,3-dichloropropene) is used as a nematicide. The synergistic activity of MITC and 1,3-D was discovered by Schering AG and the ready for use formulation of these compounds, Ditrapex (MITC 20% +1,3-D 40%) was developed in 1958.

In Japan, efficacy trials for soil fumigation with Di-trapex and Trapexide (MITC 20%) were initiated in 1970 and the efficacy was confirmed for various crops including vegetables, potatoes, ornamentals, *etc.* MITC is phytotoxic to crops and planting must be delayed until dissipation and decomposition is complete. The cress germination test should be used to ensure the absence of phytotoxic residue before planting.

In order to investigate the toxicological properties of MITC and its formulations, a number of animal toxicity studies were conducted.

The results indicate that MITC is a toxic substance and is extremely irritant to skin and mucous membranes. MITC vapours also irritate mucous membranes, and it is a strong lachrymator. Inhalation of MITC vapours may represent the main contamination risk to users. However, proper application in accordance with the recommended handling precautions, including the use of full protective clothing should not present an unacceptable hazard to users.

Chemical name: Methyl isothiocyanate

Chemical structure: CH_3–N=C=S

Molecular weight: 73.12

Appearance: colorless crystalline solid with pungent horse-radish-like odour at room temperature

Melting point: 35°C

Boiling point: 119°C

Solubility: Water 7.6 g/*l* (20°C), readily soluble in most commonly used organic solvents

Partition coefficient (*n*-octanol/water): 10.5

Vapour pressure: 20.7 mmHg at 20°C

ACUTE TOXICITY STUDIES

The LD_{50} (mg/kg body weight) or LC_{50} (g/m^3) values determined from acute toxicity studies on rat, mouse or rabbit are as follows:

Test substance	Route of administration	Rat		Mouse	
		Male	Female	Male	Female
Technical					
	Oral[1,2]	175	72	90	104
	Subcutaneous[1]	60	59	75	89
	Intraperitoneal[1]	54	56	82	89
	Dermal[2]	2780		1870	
	Inhalation[8]	1.9 (1 hr LC_{50})			
Di-Trapex					
	Oral[6]	478	472	341	344
	Oral[10]	310	321		
	Dermal[10]	473	510		
	Inhalation[8]	11 (1 hr LC_{50})			
Trapex 40 (MITC 40%)					
	Oral[17]	166			
	Dermal[18]	*ca.* 120 (rabbit)			
	Inhalation[19]	1.5 (4 hr LC_{50})			

IRRITATION STUDIES

1. Primary Dermal Irritation Study on Rabbits[18]

Decimal five-ml of Trapex 40 was applied to the intact skin of a shaved area (10 cm × 10 cm) of rabbits for a 4-hr semi-occlusive application period. The skin reaction was assessed according to the US EPA Pesticide Assessment Guidelines Paragraph 81-5.

The test article caused a primary irritation score of 4.2 under the conditions of this study. Severe corrosion effects had occurred on the skin. In the area of application, however no discoloration of the skin was observed which could be related to effects of the test article.

2. Primary Eye Irritation Studies on Rabbits[7]

Evaluation of the eye irritation properties of MITC or Di-Trapex was made using the procedure that was prescribed by The Consumer Product Safety Commission of the USA in the Code of Federal Regulations, Title 16, Section 1500. 42.

Instillation of 100 mg of the test articles produced severe inflammation including corneal opacity, iritis and conjunctival swelling.

3. Dermal Sensitization Study on Guinea Pigs[18]

The study was conducted according to the guinea pig maximization test.

Induction: An area of dorsal skin from the scapular region (approximately 8 cm × 6 cm) was clipped free of hair. Three pairs of intradermal injections (0.1 ml of a 1% dilution of Trapex 40 per site) were made at the border of a 4 cm × 4 cm area in the clipped region.

One week after the injections, the scalpular area was again clipped and shaved free of hair. A 4 cm × 4 cm patch was saturated with 1% of the test article, placed over the injection sites and removed 48 hr after application.

Challenge: Two weeks after the topical induction application, a 2 cm × 2 cm patch saturated with 1% of the test article was applied to the left flank which had been clipped and shaved (5 cm × 5 cm). The patch was removed 24 hr later.

Rechallenge: A second challenge was performed two weeks after the first challenge. The method was similar to that described for the first challenge with the exception that the right flanks were used.

The challenge sites were evaluated on the basis of Draize score just after application, 24 and 48 hr after removal of the patch.

From the result of the study, Trapex 40 is considered to possess a mild skin sensitizing potential in guinea pigs.

SUB-ACUTE AND SUB-CHRONIC TOXICITY STUDIES

1. Three-month Sub-chronic Oral Toxicity Study in Mice[3]

MITC was administered daily, orally by gavage, to dd-strain mice at dose levels of 1, 5 and 20 mg/kg body weight/day for 3 months.

The oral administration of MITC at 20 mg/kg resulted in several dose-related toxic effects (*e.g.* thickening of fore-stomach lining, small cell infiltration in liver tissues, slight disturbance of spermatogenesis with oedema of interstitial cells) in which were occasionally noted in the 5 mg/kg group and which, however, were slight at 1 mg/kg.

Both absolute and relative ovary weights showed a significant decrease but there were no microscopic changes associated with this finding even at 20 mg/kg.

2. Three-month Sub-chronic Oral Toxicity Study in Mice[4]

MITC was administered at 2.5, 5 and 10 mg/kg body weight/day by oral gavage to dd-strain mice for three months.

The only significant changes were an increase in total white blood cell counts which was shown to be due to an increase in neutrophilic leucocytes in the differential blood smears whilst the lymphocyte count was decreased at 10 mg/kg in male mice. All the findings at lower dosage groups were occasionally noted but they were spontaneous and did not give any treatment-related effect.

3. Three-month Sub-chronic Oral Toxicity Study in Mice[5]

MITC was given orally, by gavage, to Slc: ddy-strain mice at dose levels of 0.35, 0.5, 0.7 and 1.0 mg/kg body weight/day. The main objective of the study was to confirm the effect on ovaries which demonstrated by the

study mentioned above under 1.

All the parameters evaluated, however, did not show any treatment-related effects. Because of retarded body weight gain and increased liver weight in the 1 mg/kg group, the NOEL was 0.7 mg/kg body weight/day.

4. Three-month Sub-chronic Oral Toxicity Study in Rats[3]

MITC was administered at 2, 10 and 40 mg/kg body weight/day by oral gavage to Wistar rats.

Administration of MITC resulted significant toxic effects, *e.g.* stomach lesions, small round cell infiltration of liver tissues and a slight spermatogenic disorder in the 40 mg/kg group which were occasionally noted at 10 mg/kg.

In the ovaries, there was a significant increase in absolute organ weight but not in relative organ weight and there were no microscopic changes associated with the increase of the ovary weights even in the 40 mg/kg group. From the results obtained a NOEL of 2 mg/kg body weight/day was derived.

5. Three-month Sub-chronic Oral Toxicity Study in Rats[4]

MITC was administered at dose levels of 5, 10 and 20 mg/kg body weight/day by oral gavage to Wistar rats.

Oral administration of MITC resulted in an increase in white blood cells which was shown to be due to an increase in neutrophilic leucocytes in the differential blood smears whilst the lymphocyte count was decreased at 20 mg/kg.

Liver fatty change was also given. Other histopathologic changes at 20 mg/kg group and all the findings at lower dosage groups were occasionally noted but they were spontaneous and did not give any treatment-related effect.

6. One-month Sub-acute Dermal Toxicity Study in Rats[5]

The following findings were obtained from a systemic toxicity test of MITC, applied at dose levels of 120, 240 and 480 mg/kg body weight/day to shaved rat skin (Sprague Dawley strain) throughout a month in order to investigate the effects on liver, genital organs and the nervous system.

Depending upon the dose administered, modifications of the treated skin areas (ulceration, crust formation, infiltration of neutrophilic leucocytes) were noted. Changes in the genital organs or liver were sporadic and not regarded to be significant. There were no histological changes in the nervous system.

Treatment-related changes other than the treated skin were noted in the respiratory tract, characterized by enlargement of the peribronchial lymphnodes.

7. Sub-chronic Inhalation Toxicity Study in Rats[11]

In order to determine the subacute systemic inhalation toxicity of MITC, Wistar rats were exposed for 4 hr per day, five days per week, for 12–13 weeks to an atmosphere containing concentrations of approximately 1, 10 and 45 ppm of MITC (nose only chamber).

Statistically significant substance-related effects were noted in the high dose level animals only which showed toxic clinical signs (increased salivation and nasal discharge during exposure, apathy), reduced food consumption and body weight gain, as well as organ weight alterations in females. The remainder of the parameters examined did not show any substance-related effects. Accordingly a NOEL 10 ppm (30.67 mg/m^3) was derived.

CHRONIC TOXICITY/ONCOGENICITY STUDIES

1. Two-year Chronic Oral Toxicity/Oncogenicity Study in Rats[13]

MITC was administered to CD strain rats in the drinking water at dose levels of 2, 10 and 50 ppm for 104 weeks.

Male rats given 50 ppm MITC gained weight less rapidly than the controls throughout the study. Although other treatment groups, including females, gained weight less rapidly than controls, there was no evidence for a relationship with dose. Water consumption was less in treated animals than in controls, but no clear relationship between MITC concentration and the magnitude of the differences was seen. However, rats given 50 ppm MITC showed the most consistent reduction in water intake. The findings obtained from the re-

mainder of the parameters evaluated did not reveal any treatment-related effects. No oncogenic response was seen to MITC at any of the dose levels administered. From the results obtained a NOEL of 10 ppm (male; 0.514 mg/kg/day, female; 0.746 mg/kg/day) can be derived.

2. Two-year Chronic Oral Toxicity/Oncogenicity Study in Mice[12]

MITC was administered to ICR: JCR mice in the drinking water at dose levels of 5, 20, 80 and 200 ppm for 106 weeks.

Both males and females of the 80 and 200 ppm groups showed reduced treatment-related body weight gains. Although some changes were noted for water intake, haematology, clinical chemistry and urinalysis, there was no clear relationship with administration of MITC. The slight changes in absolute and relative organ weights noted in the 80 and 200 ppm groups are considered to reflect the reduced body weight gains in these groups. Mortality, general behaviour, food consumption and efficiency, as well as ophthalmoscopic findings from treated animals compared well with untreated controls. Necropsy, histopathological examinations, tumor profile and incidence did not reveal any treatment-related abnormal findings, but showed a pattern usual in mice in view of their age. MITC did not give an oncogenic effect at any of the dose levels administered. Therefore, it is concluded that the LEL was 80 ppm and the NOEL was 20 ppm (male; 3.30 mg/kg/day, female; 3.66 mg/kg/day).

REPRODUCTIVE AND FERTILITY EFFECTS, AND TERATOGENICITY STUDIES

1. Two Generation Reproduction Study in Rats[16]

MITC was administered to Sprague Dawly CD rats in the drinking water at dose levels of 2, 10 or 50 ppm. The F_0 generation were treated for a 70 day maturation period before mating to produce F_{1a} litters which were reared to weaning. F_1 generation animals were selected from F_{1a} offsprings at weaning. F_1 generation animals were treated for 77 days prior to pairing to produce F_{2a} litters which were reared to weaning.

MITC did not have any adverse effects on fertility, reproductive performance of the parental animals and on viability, growth and development of the offspring. Toxicity to the adults comprised a reduction in body weight gain of F_1 males at 50 ppm.

The dose-related reduction in water consumption at 10 and 50 ppm group was considered to reflect the unpalatability of the test article which was administered via the drinking water. The NOEL for toxicity was 10 ppm.

2. Teratogenicity Study in Rats[14]

Pregnant rats were treated orally with MITC, by gavage, at 1, 5 or 25 mg/kg body weight daily from day 6 to day 15 of gestation, inclusive.

Administration of MITC at 25 mg/kg resulted in a significant reduction in food intake with a corresponding reduction in body-weight gain. Irritation of the mucosal surface of the stomach and visceral adhesion were also observed at this dose level. Despite the maternal toxicity, there was no effect of MITC treatment at any dose level on pregnancy incidence, implantations, pre- or post-implantation loss or on foetal numbers or sex distribution. At 25 mg/kg there was evidence of embryonic growth retardation, but this was considered to be a secondary effect of the marked maternal growth retardation and not a direct effect of treatment with MITC. MITC did not elicit embryolethality or teratogenicity. The NOEL with regard to any aspect of foetal development established in this study was 5 mg/kg/day.

3. Teratogenicity Study in Rabbits[15]

New Zealand white rabbits were treated orally with MITC by gavage at 1, 3 or 5 mg/kg body weight from day 7 to day 19 of gestation, inclusive.

Administration of 5 mg/kg MITC elicited minimal maternal toxicity characterised by effects on food consumption and body weight. As a consequence of this maternal toxicity there was a slight degree of embryonic growth retardation. There was however, no effect on embryolethality and no evidence of teratogenicity.

The remainder of the parameters examined did not reveal any treatment-related effects. From the results obtained, the NOEL for fetotoxic effects was 3 mg/kg.

MUTAGENICITY STUDIES

1. Rec-assay/Reverse Mutation Test[10]

MITC was tested for a possible mutagenic effect in microbial systems, including the Rec-assay for potential DNA-damage utilizing H 17 rec^+ and M 45 rec^- strains of *Bacillus subtilis*, and the reverse mutation tests with and without a liver metabolic activation system employing *Escherichia coli* WP2 *hcr* and *Salmonella typhimurium* strains (TA 1535, TA 1537, TA 1538, TA 100 and TA 98).

In all the test systems used MITC was not mutagenic.

2. Forward Mutation Assay[20]

MITC was tested for possible mutagenic effects in the hypoxanthine-guanine phosphoribosyl transferse (HGPRT) system using Chinese hamster cell line V79. A range of 4 concentrations was applied to the cell cultures, starting at 1.00 μg/ml without S9-mix and 2.5 μg/ml with S9-mix, and diluting in two-fold steps.

MITC did not show any reproducible enhancement of the mutation rate over the negative control range, either with or without metabolic activation with S9-mix. The results showed that MITC was not mutagenic in the HGPRT-test with V79 cells.

3. Structural in vitro Chromosome Aberration Test[20]

MITC was tested for a possible mutagenic effect by assessing structural aberration rates in the chromosomes of Chinese hamster cell line V79.

Cells were exposed to MITC at concentrations of 0.1, 0.5 or 1 μg/ml without S9-mix, or 0.25, 0.75 or 2.5 μg/ml with S9-mix. The number of chromosomes per metaphase was determined at 6, 12 and 28 hr after the start of a 4 hr treatment.

MITC induced chromosomal aberrations, especially breaks and exchanges in V79 cells treated with 1.0 μg/ml without S9-mix and at 2.5 μg/ml with S9-mix and prepared 28 hr after the treatment. These concentrations were also cytotoxic. MITC must be classified as mutagenic in this *in vitro* chromosome aberration test with V79 cells.

4. Structural in vitro Chromosome Aberration Test[24]

MITC was assessed for its potential to induce structural chromosome aberrations in human lymphocytes *in vitro*.

Chromosome preparation was conducted 24 and 48 hr after start of treatment with MITC. The treatment interval was 4 hr. Cell cultures were exposed to MITC at concentrations of 3.0 or 5.0 μg/ml both in the presence or absence of S9-mix.

There was no biologically relevant increase in cells with aberrations after treatment with MITC at any interval or concentration, with or without S9-mix. MITC was therefore not mutagenic in the *in vitro* chromosome aberration test in human lymphocytes.

5. Micronucleus Test in Mice[9]

MITC was administered to CD-1 mice by gavage at a single dose of 110 mg/kg body weight which would be expected to kill approximately 10% of the animals within 72 hr of dosing. Bone marrow smears were obtained 24, 48 and 72 hr after dosing.

No significant increase in the frequency of micronucleated polychromatic erythrocytes was seen in mice treated with MITC at any of the sampling times. At 24 hr, the ratio of polychromatic to normochromatic erythrocytes in MITC-treated animals was comparable with the controls. At 72 hr and, especially 48 hr, the ratio was significantly lower. These lowered ratios are considered to be indicative of cytotoxicity to the bone marrow cells. It is concluded that MITC showed no evidence of mutagenic potential when administered to mice by gavage in this *in vivo* micronucleus test.

6. Unscheduled DNA Synthesis Assay[21]

This assay used rat primary hepatocyte was based on the procedures described by Williams (1977, 1980).

A range of 8 concentration of MITC was applied to the cell cultures, starting at 30.3

μg/ml and diluting in approximately two-fold steps to 0.253 μg/ml. Treatment was initiated by replacing the medium on the cell cultures with Williams' Medium E (1% serum) containing MITC at the desired concentrations. Treatment with 30.3 μg/ml of MITC was completely lethal. MITC did not induce significant changes in the nuclear labelling of primary rat hepatocytes within the applied concentration range of 15.2 to 0.253 μg/ml. Therefore, MITC was evaluated as inactive in the UDS assay.

7. Sister Chromatid Exchange Assay[24]

MITC was assessed for its potential to induce sister chromatid exchanges in Chinese hamster V79 cell *in vitro*. The study was performed in two independent experiments, two parallel cultures being used per experimental group. Twenty-five metaphases per culture were scored for SCEs. Dose levels of MITC used were 0.1, 2.0 and 3.5 μg/ml without S9-mix and 0.1, 2.5 and 5.0 μg/ml with S9-mix. Chromosomes were prepared 24 hr after addition of BrdU and 28 hr after start of treatment, respectively.

The treatment at 2.0 μg/ml clearly reduced the plating efficiency of the V79 cells although the replication index was suppressed only after treatment at the top dose levels with or without S9-mix in both experiments.

In both experiments, there were no reproducible increase in cells with SCEs at any dose level with or without metabolic activation. MITC was therefore not mutagenic under the conditions of this test system.

GENERAL PHARMACOLOGY[22,23]

1. Effects on the Central Nervous System

Mice or rabbits were administered 10, 30 or 100 mg/kg body weight of MITC by oral gavage and the mice were observed following Irwin procedure while rabbits were observed for clinical signs.

Marked excitating action was observed at the lethal dose of 100 mg/kg, and it was slight at 30 mg/kg, but not noted at 10 mg/kg in mice.

In rabbits, no excitating action was observed but marked intoxication such as hypopnea and flaccid muscle were observed at 100 mg/kg which led to death. These symptoms were mild at 30 mg/kg while no intoxication was observed at 10 mg/kg.

At necropsy, congestion and heamorrhage were found in the stomach and intestine of the dead mice and rabbits.

2. Effect on Autonomic Nervous System and Smooth Muscle

2.1 Effect on spontaneous motility of isolated ileum

The ileum isolated from rabbits was suspended in an air-supplied organ bath filled with Tyrode solution and spontaneous motility was recorded. Final concentration of MITC in the Tyrode solution was adjusted from 3.8×10^{-8} to 3.8×10^{-5} g/ml.

MITC showed a reduced contraction rate on the isolated ileum at 3.8×10^{-5} g/ml, a slight inhibitory action at 3.8×10^{-7} g/ml and no action at 3.8×10^{-8} g/ml.

2.2 Antagonist action of MITC

The ileum isolated from guinea pigs was suspended in the same manner as described above. Antagonist action of MITC against acetylcholine, histamine and barium chloride was determined three minutes after the addition of MITC.

Final concentrations of MITC in the Tyrode solution was 3.8×10^{-7}–3.8×10^{-5} g/ml.

Slight inhibition was observed on acetylcholine-induced contractions at the concentration of 3.8×10^{-5} g/ml, whilst no action was observed on the histamine-induced contraction up to the concentration of 3.8×10^{-5} g/ml. A prolongation was observed in reaction time of the barium chloride-induced contractions, and a tendency to enhancement of contraction was observed thereafter.

2.3 Effect on gastro-intestinal propulsion

Activated charcoal suspension was given orally to mice 30 min after the oral administration of MITC at 10, 30 or 100 mg/kg body weight. Thirty minutes after administration of the suspension, the animals were sacrificed and propulsion of the charcoal to the small intestine determined.

No action of MITC was observed either in the 10 mg/kg or in the 30 mg/kg group. In the 100 mg/kg group, significant inhibition was observed in the propulsion of activated charcoal.

3. Effect on Respiratory and Circulatory Systems

One hundred-mg/kg of MITC was administered orally to cats under anesthesia and respiration, blood pressure, heart rate and electrocardiogram (ECG) were monitored from before administration of MITC until cardiac arrest occurred after the administration.

The oral administration of 100 mg/kg MITC increased blood pressure immediately after administration, and then blood pressure gradually decreased in direct relation to the decrease in pulse pressure. Heart rate increased from 60 min to 90 min after administration of MITC, and ECG showed a decrease in voltage of QRS, 10 to 15 min after administration.

There were no marked changes in voltage of P and T waves, but slight changes in PR and QT intervals were observed in proportion to the changes in heart rate. Although respiration did not show marked changes until 90 min after administration, it suddenly became slow and stopped 120 min after administration, followed by cardiac arrest. Autopsy studies did not reveal any serious toxic effects of MITC on the gastro-intestinal tract.

As it was considered that MITC affected cardiac functions, noradrenaline which was effective in enhancing cardiac function, glutathione which is implicated in the metabolism of MITC, and sodium thiosulfate a cyanide antidote were used to investigate the mechanisms of their detoxifying action on MITC poisoning. These drugs were administered continuously to cats following oral treatment with MITC.

Noradrenaline slightly delayed the time when respiration stopped followed by cardiac arrest, but it did not correct abnormal changes in blood pressure and ECG caused by MITC. Glutathione did not delay respiratory arrest nor alleviate MITC's toxic effects. MITC's toxic effects were not affected by sodium thiosulfate, either.

4. Effect on Blood

4.1 Effect on blood coagulation in vivo

Blood samples were collected from the abdominal aorta of rats under anesthesia one hour after the oral administration of MITC at 10, 30 or 100 mg/kg. Prothrombin time (PT) and activated partial thromboplastin time (APTT) were determined using the plasma samples.

No effect of MITC was observed on PT or APTT at any of the dose levels. No abnormality was seen in the color of the collected venous blood.

4.2 Effect on heamolysis in vitro

Blood samples were collected from the auricular vein of rabbits and a suspension of erythrocytes was prepared. Heamolysis were checked by addition of a suspension into the MITC solution.

No heamolysis was observed at concentrations of 0.0076% or 0.076% MITC, whilst only slight heamolysis was observed at 0.76%.

5. Conclusion

From these results, it is considered that the lethal factor in intoxication caused by MITC is cardiac toxicity. However, the toxic action was observed only when MITC was given in high doses close to the lethal dose, so that cardiac toxicity might not be a specific compound-related pharmacological action. It is difficult to elucidate a detoxification mechanism from the results obtained. Consequently, it is considered to be appropriate at present to employ symptomatic and supportive treatment in cases of intoxication caused by MITC.

SUMMARY

In order to investigate the toxicological properties of MITC and its formulations, a number of animal toxicity studies were conducted. In conclusion MITC is a toxic substance and shows severe corrosive effects and inflammation to skin and mucous membranes. In addition, it's vapours irritate mucous membranes and are lachrymatory.

In a sensitization test in guinea pig, the test substance showed a mild skin sensitizing potential. In sub-chronic studies administered by oral gavage to rats and mice, MITC gave considerable dose-related toxic effects (*e.g.* stomach lesions, small round cell infiltration of the liver, slight spermatogenic disorder, decreased body weight gain, decreased ovary weight in mice, *etc.*) particularly at higher doses. A repeat study on mice to assess the effect on ovaries did not give any treatment-

related effects in these organs. Long term chronic oral toxicity/oncogenicity studies in which MITC was administered to rats or mice in the drinking water, did not show any of the dose-dependent or substance-related effects that had been found in the sub-chronic studies. The only significant changes in the long term studies were a decreased body weight gain and water consumption in the high dose groups.

MITC showed no oncogenic activity and had no adverse effect on reproductive capacity or in teratogenicity studies. In a number of mutagenicity studies, Rec-assay, reverse mutation, mouse micronucleus test, unscheduled DNA synthesis, sister chromatid exchange and forward mutation, MITC was negative although a *in vitro* chromosome aberration in Chinese hamster's cells was positive. Whilst in human lymphocytes it was negative. Di-Trapex and Trapexide were initially registered as soil fumigants in 1976 and 1982, respectively.

Withholding values for registration have been set at 0.05 ppm on fruits, 0.2 ppm on vegetables and tea, and 0.5 ppm on potatoes. MITC is a toxic substance with severe irritant effects on skin and mucous membranes, therefore, proper application in accordance with the recommended handling precautions including the use of full protective clothing must be followed. Then products containing MITC may not only be useful but also safe to users and applicators.

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Test sites and reported year

1) Matsumoto Dental College, 1974
2) Tokyo Dental College, 1970
3) Toho University, 1970
4) Tokushima University, 1972
5) Nara Prefectural Medical College, 1974
6) Shionogi & Co., Research Laboratories, 1975
7) Huntingdon Research Centre, 1976
8) Huntingdon Research Centre, 1977
9) Huntingdon Research Centre, 1985
10) The Institute of Environmental Toxicology, 1978
11) Schering AG, 1978
12) Nippon Experimental Medical Research Institute, Keio University, Sasaki Research Laboratories, Tokyo Denryoku Hospital; 1980
13) Hazleton Laboratories Europe, 1981
14) Hazleton Laboratories Europe, 1983
15) Hazleton Laboratories Europe, 1984
16) Hazleton Laboratories Europe, 1987
17) Research & Consulting Co., 1984
18) Research & Consulting Co., 1985
19) Research & Consulting Co., 1986
20) Technische Hochschule Darmstadt, 1984
21) Litton Bionetics, 1985
22) Biological Research Center for Protection of Environmental, 1986
23) Biological Research Center for Protection of Environmental, 1987
24) Cytotest Cell Research GmbH & Co., KG, 1988