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Item 5 (b) of the provisional agenda*

Inclusion of chemicals in Annex III of the Rotterdam Convention: review of notifications of final regulatory actions to ban or severely restrict a chemical: methyl parathion

Methyl parathion: supporting documentation provided by Bulgaria

Note by the secretariat

The annexes to the present note contain the supporting documentation provided by Bulgaria in support of its final regulatory action on methyl parathion.

* UNEP/FAO/RC/CRC.2/1.

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Annex

List of supporting documentation on methyl parathion from Bulgaria

Focused summary on methyl parathion from Bulgaria

I. Introduction

(a) The events that led to the final regulatory action;

Methyl parathion was excluded from the list of active substances authorized for use in plant protection products in 1991 according to the *Law on protection of plants against pests and blights*, as a result of a review of the chemical conducted by the National Service for Plant Protection (NSPP) at the Ministry of Agriculture and Forestry in cooperation with the National Centre for Hygiene, Medical Ecology and Nutrition at the Ministry of Health.

(b) Significance of regulatory action, e.g. one use or many uses, level or degree of exposure;

All formulations and uses of *Methyl parathion* have been prohibited except the import and use of the chemical for research or laboratory purposes in quantities less than 10 kg according to the *Regulation on the import and export of certain dangerous chemicals on the Bulgarian territory (SG 63 of 20 July 2004, in force since 1st January 2005).*

(c) Scope of the regulatory action– precise description of the chemicals subject to the regulatory action.

According to Joint Order № RD 09-130/13.03.2003 of the Minister of Agriculture and Forestry; RD 09-98/25.02.2003 of the Minister of Health; RD-228/07.03.2003 of the Minister of Environment and Water, related to the approval of a list of active ingredients banned for use in plant protection products under Article 15g of Plant Protection Act, **it is prohibited to use and place on the market** all plant protection products containing *Methyl parathion* according to the provisions of *Directive 79/117/EEC of 21 December 1978 prohibiting the placing on the market and use of plant protection products containing certain active substances.*

II. Risk evaluation

A specific national risk/hazard evaluation was not performed in 1991. The decision to ban the chemical was taken after an examination of the available scientific risk data on *Methyl parathion* published by other countries/organizations, in the context of the prevailing conditions in our country during that period. The final regulatory action was undertaken in 2003 as a result of the process of harmonization of the national legislation with the EU requirements in the field of plant protection products.

III. Supporting documentation

1. Relevant documentation for Section 2.4.1, referring to protecting human health

   See Annex I to this document.

2. Relevant documentation for Section 2.4.2, referring to protecting the environment

   See Annex II to this document.

Annex I

Extension Toxicology Network (EXTOXNET)

P**esticide **I**nformation **P**rofile of **Methyl Parathion

Publication Date: 5/94

(Extract)

Acute toxicity

Methyl parathion is highly toxic by inhalation and ingestion, and moderately toxic by dermal adsorption (9). As with all organophosphates, methyl parathion is readily absorbed through the skin. Skin which has come in contact with this material should be washed immediately with soap and water and all contaminated clothing should be removed. Accidental skin and inhalation exposure to methyl parathion have caused human fatalities. Methyl parathion may cause contact burns to the skin or eyes (13).

Because methyl parathion has a short half-life (1 hour on cotton) when applied to crops, the risk of exposure to agricultural workers is low. Factory workers who handle quantities of concentrated methyl parathion are at a higher risk (2). Exposure may occur during mixing, spraying or application of methyl parathion, during cleaning and repair of equipment or during early re-entry into fields (20). Persons with respiratory ailments, recent exposure to cholinesterase inhibitors, cholinesterase impairment, or liver malfunction are at increased risk from exposure to methyl parathion. High environmental temperatures or exposure of the chemical to visible or UV light may increase its toxicity (9).

The organophosphate insecticides are cholinesterase inhibitors. They are highly toxic by all routes of exposure. When inhaled, the first effects are usually respiratory and may include bloody or runny nose, coughing, chest discomfort, difficult or short breath, and wheezing due to constriction or excess fluid in the bronchial tubes. Skin contact with organophosphates may cause localized sweating and involuntary muscle contractions. Eye contact will cause pain, bleeding, tears, pupil constriction, and blurred vision. Following exposure by any route, other systemic effects may begin within a few minutes or be delayed for up to 12 hours. These may include pallor, nausea, vomiting, diarrhea, abdominal cramps, headache, dizziness, eye pain, blurred vision, constriction or dilation of the eye pupils, tears, salivation, sweating, and confusion. Severe poisoning will affect the central nervous system, producing incoordination, slurred speech, loss of reflexes, weakness, fatigue, involuntary muscle contractions, twitching, tremors of the tongue or eyelids, and eventually paralysis of the body extremities and the respiratory muscles. In severe cases there may also be involuntary defecation or urination, psychosis, irregular heart beats, unconsciousness, convulsions and coma. Death may be caused by respiratory failure or cardiac arrest (9).

Some organophosphates may cause delayed symptoms beginning 1 to 4 weeks after an acute exposure which may or may not have produced immediate symptoms. In such cases, numbness, tingling, weakness and cramping may appear in the lower limbs and progress to incoordination and paralysis. Improvement may occur over months or years, but some residual impairment will remain (9).

The amount of a chemical that is lethal to one-half (50%) of experimental animals fed the material is referred to as its acute oral lethal dose fifty, or LD50. The oral LD50 for methyl parathion in rats is 18 to 50 mg/kg, in mice is 14.5 to 19.5 mg/kg, in rabbits is 420 mg/kg, in guinea pigs is 1270 mg/kg, and in dogs is 90 mg/kg (2, 3, 9). The dermal LD50 in rats is 63 to 491 mg/kg, in mice is 1200 mg/kg, and in rabbits is 300 mg/kg (3, 9)

The lethal concentration fifty, or LC50, is that concentration of a chemical in air or water that kills half of the experimental animals exposed to it for a set time period. The 4-hour inhalation LC50 for methyl parathion in rats is 34 mg/m3, and in mice is 120 mg/m3 (9).

Chronic Toxicity

Repeated or prolonged exposure to organophosphates may result in the same effects as acute exposure including the delayed symptoms. Other effects reported in workers repeatedly exposed include impaired memory and concentration, disorientation, severe depressions, irritability, confusion, headache, speech difficulties, delayed reaction times, nightmares, sleepwalking and drowsiness or insomnia. An influenza-like condition with headache, nausea, weakness, loss of appetite, and malaise has also been reported (9).

Studies with human volunteers have found that 1 to 22 mg/person/day have no effect on cholinesterase activity. In a 4-week study of volunteers given 22, 24, 26, 28 or 30 mg/person/day, mild cholinesterase inhibition appeared in some

individuals in the 24, 26 and 28 mg dosage groups. In the 30 mg/person/day (about 0.43 mg/kg/day) group, red blood cholinesterase activity was depressed by 37%. When methyl parathion was fed to dogs for 12 weeks, a dietary level of 1.25 mg/kg soon caused a significant depression of red blood cell and plasma cholinesterase. A dietary level of 0.125 mg/kg produced no effects (2).

The EPA has established a Lifetime Health Advisory (LHA) level of 60 micrograms per liter (ug/l) for 4-nitrophenol, a breakdown product of methyl parathion, in drinking water. This means that EPA believes that water containing 4-nitrophenol at or below this level is acceptable for drinking every day over the course of one's lifetime, and does not pose any health concerns. However, consumption of 4-nitrophenol at high levels well above the LHA level over a long period of time has been shown to cause adverse health effects, including damage to the liver, respiratory stress, and inflammation of the stomach in animal studies (11).

Reproductive Effects

In a 3-generation study with rats fed dietary levels of 0, 0.5, or 1.5 mg/kg/day, there was reduced weanling survival, reduced weanling weights, and an increase in the number of stillbirths at the 1.5 mg/kg. Some of these effects also occurred at the 0.5 mg/kg dosage level. In rats and mice, a single injection of LD50 rates during pregnancy caused suppression of fetal growth and bone formation in the offspring that survived. These injections also caused high fetal mortality. The rats had been injected with 25 mg/kg on day 12 of pregnancy, and the mice were injected with 60 mg/kg on day 10. In another study, there were no adverse effects observed in the offspring of rats given oral doses of 4 or 6 mg/kg on day 9 or 15 of pregnancy (2). Once in the bloodstream, methyl parathion may cross the placenta (9). Large doses of methyl parathion injected into pregnant rats and mice reduced litter size and survival of offspring (6).

Teratogenic Effects

Methyl parathion is a possible human teratogen (14).

Mutagenic Effects

No signs of mutagenicity were seen in mice given dosages of 5 to 100 mg/kg, nor in mice fed methyl parathion for 7 weeks (2). No mutagenic changes were seen when cell cultures were grown from factory workers who had been exposed to low levels of methyl parathion for very long periods of time (15, Mut. Res. 103 (1):71-76. 1982). Other research has shown mutations to occur in cells exposed to methyl parathion (Mut. Res. 102 (1):89-102. 1982).

Carcinogenic Effects

Methyl parathion is not a suspected carcinogen (20, 21).

Organ Toxicity

Methyl parathion primarily affects the nervous system through inhibition of cholinesterase, an enzyme required for proper nerve functioning (9).

Consumption of 4-nitrophenol, a breakdown product of methyl parathion, at high levels well above the Lifetime Health Advisory level of 60 ug/l over a long period of time has been shown to cause adverse health effects, including damage to the liver, respiratory stress, and inflammation of the stomach in animal studies (11).

Fate in Humans and Animals

Methyl parathion is rapidly absorbed into the bloodstream through all normal routes of exposure. Following administration of a single oral dose, the highest concentration of methyl parathion in body tissues occurred within 1 to 2 hours (2). Metabolism occurs in the liver, eventually to phenols which can be detected in the urine (14). Methyl parathion does not accumulate in the body. It is almost completely excreted through the kidneys (urine) within 24 hours (8).

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Annex II

IPCS INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY
Health and Safety Guide No. 75, GENEVA 1992
Methyl Parathion
(Extract)

2.1 Environmental exposure

The distribution of methyl parathion in air, water, soil, and in organisms in the environment is influenced by several physical, chemical, and biological factors.

Studies using model ecosystems and mathematical modeling indicate that methyl parathion partitions mainly to air and soil in the environment, with lesser amounts in plants and animals. There is virtually no movement through soil and neither the parent compound nor its breakdown products will reach ground water. Methyl parathion in air is mainly derived from spraying of the compound, though some volatilization occurs with the evaporation of water from leaves and the soil surface. Background atmospheric levels of methyl parathion in agricultural areas range from not detectable to about 70 ng/m^3. Air concentrations after spraying declined rapidly over 3 days and returned to background levels after about 9 days. Levels in river water (in laboratory studies) declined to 80% of the initial concentration after 1 h and 10% after 1 week. Methyl parathion is retained longer in soil than in air or water, though retention is greatly influenced by soil type; sandy soil can lose residues of the compound more rapidly than loams. Residues on plant surfaces and within leaves decline rapidly with half-lives of the order of a few hours; complete loss of the methyl parathion occurs within about 6-7 days.

Animals can degrade methyl parathion and excrete the degradation products within a very short time. However, this occurs more slowly in lower vertebrates and invertebrates than in mammals and birds. Bioconcentration factors are low and the accumulated methyl parathion levels transitory.

By far the most important route for the environmental degradation of methyl parathion is microbial degradation. Loss of the compound in the field and in model ecosystems is more rapid than predicted from laboratory studies. This is because of the presence of a variety of microorganisms capable of degrading the compound in different habitats and circumstances. When sediment or plant surfaces are present, the microbial populations increase with a resulting increase in the rate of breakdown of methyl parathion. Methyl parathion can undergo oxidative degradation, to the less stable methylparaoxon, in the presence of ultraviolet radiation (UVR) or sunlight; sprayed films degrade under UVR with a half-life of about 40 h. However, the contribution of photolysis to total loss in an aquatic system was estimated to be only 4%. Hydrolysis of methyl parathion also occurs and is more rapid under alkaline conditions. High salinity also favours hydrolysis of the compound. Half-lives of a few minutes were recorded in strongly reducing sediments though methyl parathion is more stable when sorbed on other sediments.

In towns in the centre of agricultural areas of the USA, methyl parathion concentrations in air varied with season and peaked in August or September; maximum levels in surveys were mainly in the range of 100-800 ng/m^3, during the growing season. Concentrations in natural waters of agricultural areas in the USA ranged up to 0.46 µg/litre with highest levels in summer. There are only a small number of published reports on the residues of methyl parathion in food throughout the world. In the USA, residues of methyl parathion in food have generally been reported at very low levels with few individual samples exceeding maximum residue limits (MRLs). Only trace residue levels of methyl parathion have been detected in the total dietary studies reported. Methyl parathion residues were highest in leafy (up to 2 mg/kg) and root vegetables (up to 1 mg/kg) in market basket surveys in the USA between 1966 and 1969. Food preparation, cooking, and storage all cause decomposition of methyl parathion residues further reducing human exposure. Raw vegetables and fruits may contain higher residues after misuse.

The production, formulation, handling, and use of methyl parathion as an insecticide are the main potential sources of human exposure. Skin contact and, to a lesser degree, inhalation are the main routes of exposure of workers. In a study of farm spray-men (with unprotected workers and ULV hand-spray) an intake of 0.4-13 mg methyl parathion (per 24 h) was calculated from the *p*-nitrophenol excreted in the urine.

Early re-entry into treated crops is a further source of exposure. The general population may be exposed to air-, water- and food-borne residues of methyl parathion as a consequence of agricultural or forestry practices, and the misuse of the agent resulting in contamination of fields, crops, water, and air through off-target spraying.

2.2 Uptake, metabolism, and excretion

Methyl parathion is readily absorbed via all routes of exposure (oral, dermal, and inhalation) and is rapidly distributed to the tissues of the body. Maximum concentrations in various organs were detected 1-2 h after treatment. Conversion of methyl parathion to methylparaoxon occurs within minutes following administration. In dogs, a mean terminal half-life of 7.2 h was determined following i.v. administration of methyl parathion. The liver is the primary organ of metabolism and detoxification. Methyl parathion or methylparaoxon are mainly detoxified in the liver by oxidation, hydrolysis, and demethylation or dearylation with reduced glutathione (GSH). The reaction products are *O*-methyl- *O*-*p*-nitrophenyl phosphorothioate or dimethyl phosphorothioic or dimethylphosphoric acids and *p*-nitrophenol. Therefore, it is possible to estimate the exposure by measuring the urinary excretion of *p*-nitrophenol. The urinary excretion of *p*-nitrophenol was 60% within 4 h and approximately 100% within 24 h. The metabolism of methyl parathion is important for species selective toxicity, and the development of resistance. The elimination of methyl parathion and metabolic products occurs primarily via the urine. Studies conducted with radiolabelled ^{32}P-methyl parathion revealed, after 72 h, 75% of radioactivity in the urine and up to 10% radioactivity in the faeces.

2.3 Effects on organisms in the environment

Microorganisms can use methyl parathion as a carbon source and studies on a natural community showed that concentrations of up to 5 mg/litre increased biomass and reproductive activity. Bacteria and actinomycetes showed a positive effect of methyl parathion while fungi and yeasts were less able to utilize the compound. A 50% inhibition of growth of a diatom occurred at about 5 mg/litre. Cell growth of unicellular green algae was reduced by between 25 and 80 µg methyl parathion/litre. Populations of algae became tolerant after exposure for several weeks.

Methyl parathion is highly toxic for aquatic invertebrates, most LC_{50}s ranging from <1 µg to about 40 µg/litre. A few arthropod species are less susceptible. The no-observed-effect level for the water flea *(Daphnia magna)* is 1.2 µg/litre. Molluscs are much less susceptible with LC_{50}s ranging between 12 and 25 mg/litre.

Most fish species in both fresh and sea water have LC_{50}s between 6 and 25 mg/litre, a few species being substantially more or less sensitive to methyl parathion. The acute toxicity of amphibians is similar to that of fish.

Population effects have been seen in communities of aquatic invertebrates in experimental ponds treated with methyl parathion. The concentrations needed to cause these effects would occur only with overspraying of water bodies and, even then, would last for only a short time. Population effects are, therefore, unlikely to be seen in the field. Kills of aquatic invertebrates would be unlikely to lead to lasting effects.

Care should be taken to avoid the overspraying of ponds, rivers, and lakes, when using methyl parathion. The compound should never be sprayed in windy conditions.

Methyl parathion is a non-selective insecticide that kills beneficial species as readily as pests. Kills of bees have been reported following the spraying of methyl parathion. Effects on bees in methyl parathion incidents were more severe than those of other insecticides. Africanized honey bees are more tolerant of methyl parathion than European strains.

Methyl parathion was moderately toxic for birds in laboratory studies, acute oral LD_{50}s ranging between 3 and 8 mg/kg body weight. Dietary LC_{50}s ranged from 70 to 680 mg/kg diet. There is no indication that birds would be adversely affected from the recommended usage of methyl parathion in the field.

Extreme care must be taken to time methyl parathion spraying to avoid adverse effects on honey bees.

2.4 Effects on experimental animals and *in vitro* test systems

Oral LD_{50} values of methyl parathion in rodents range from 3 to 35 mg/kg body weight and dermal LD_{50} values from 44 to 67 mg/kg body weight.

Methyl parathion poisoning causes the usual organophosphate cholinergic signs attributed to accumulation of acetylcholine at nerve endings. Methyl parathion becomes toxic when it is metabolized to methylparaoxon. This conversion is very rapid. No indications of organophosphorus-induced delayed neuropathy (OPIDN) have been observed.

Technical methyl parathion was found not to have any primary eye or skin irritating potential.

In short-term toxicity studies using various routes of administration on the rat, dog, and rabbit, inhibition of plasma, red blood cells, and brain ChE and related cholinergic signs were observed. In a 12-week feeding study on dogs, the no-observed-adverse-effect level (NOAEL) was 5 mg/kg diet (equivalent to 0.1 mg/kg body weight per day). In a 3-week dermal toxicity study on rabbits, the no-observed-effect level (NOEL) was 10 mg/kg body weight per day. Inhalation exposure for 3weeks indicated a NOEL of 0.9 mg/m^3 air. At 2.6 mg/m^3, only slight inhibition of plasma ChE was observed.

Long-term toxicity/carcinogenicity studies were carried out on mice and rats. The NOEL in rats was 0.1 mg/kg body weight per day, based on ChE inhibition. There is no evidence of carcinogenicity in mice and rats, following long-term exposure. In another 2-year study on rats, however, there was evidence of a peripheral neurotoxic effect at a dose of 50 mg/kg diet.

Methyl parathion has been reported to have DNA alkylating properties *in vitro.*

Most of the results of *in vitro* genotoxicity studies on both bacterial and mammalian cells were positive, while 6 *in vivo* studies using 3 different test systems produced equivocal results.

In reproduction studies, at toxic dose levels (ChE inhibition), there were no consistent effects on litter sizes, number of litters, survival rates of pups, and lactation performance. No primary teratogenic or embryotoxic effects were noted.

Conclusions

Methyl parathion is not persistent in the environment. It is not bioconcentrated and is not transferred through food-chains and is degraded rapidly by many microorganisms and other forms of wildlife. It is only likely to cause damage to ecosystems in instances of heavy overexposure resulting from misuse or accidental spills. However, pollinators and other beneficial insects are at risk from spraying with methyl parathion.