3. EVALUATION OF DATA FOR ACCEPTABLE DAILY INTAKE AND ACUTE REFERENCE DOSE FOR HUMANS

3.1 DIAZINON (22)

TOXICOLOGY

Diazinon is the common name approved by the International Organization for Standardization (ISO) for *O*,*O*-diethyl *O*-2-isopropyl-6-methylpyrimidin-4-yl phosphorothioate (International Union of Pure and Applied Chemistry [IUPAC]), with the Chemical Abstracts Service (CAS) number 333-41-5.

Diazinon is a contact organophosphorus insecticide with a wide range of insecticidal activity. It is effective against adult and juvenile forms of flying insects, crawling insects, acarians and spiders. Diazoxon, the biologically active metabolite of diazinon, inhibits the activity of cholinesterases.

Diazinon is used mainly as a pesticide in agriculture and as a drug in veterinary medicine. Thus, the major source of diazinon residues in edible crops is from its use as an agricultural pesticide; residues in meat, offal and other animal products arise from its use as a veterinary drug containing active ingredient.

Diazinon has been evaluated by JMPR on several occasions since the first evaluation in 1963. In the most recent evaluation, in 2006, the Meeting established an ADI of 0–0.005 mg/kg body weight (bw), based on a no-observed-adverse-effect level (NOAEL) of 0.5 mg/kg bw per day for inhibition of erythrocyte acetylcholinesterase activity in a 92-day repeated-dose toxicity study in rats. The 2006 Meeting reaffirmed the ARfD of 0.03 mg/kg bw, established by the 2001 JMPR, based on a NOAEL of 2.5 mg/kg bw observed in a study of acute neurotoxicity in rats.

Diazinon was scheduled within the periodic review programme of CCPR for 2021. The compound was placed on the agenda by the JMPR Secretariat following the recommendation of an electronic task force of the WHO Core Assessment Group on Pesticide Residues that it be re-evaluated due to public health concerns identified by IARC and the availability of a significant number of new studies.

The current Meeting evaluated all previously considered toxicological data in addition to new published or unpublished toxicological studies and published epidemiological studies on cancer outcomes. Several study reports evaluated at previous JMPR meetings were not available to the present Meeting, as they were not submitted in the sponsor's dossier; for these studies, the evaluations in this report were summarized from the 1993 JMPR monograph without further review.

All critical unpublished studies contained statements of compliance with good laboratory practice (GLP), unless otherwise specified. The studies on human volunteers were conducted in accordance with the principles expressed in the Declaration of Helsinki or equivalent ethical standards.

Biochemical aspects

Following oral administration to rats, diazinon was almost completely absorbed and rapidly eliminated, mainly in the urine. There was no evidence of accumulation.

Diazinon is metabolized by P450 to diazoxon, the active metabolite. The main degradative pathway includes the oxidase/hydrolase-mediated cleavage of the ester bond, leading to the pyrimidinol derivative 2-isopropyl-6-methyl-4(1*H*)-pyrimidinone, which is further oxidized to more polar metabolites.

Toxicological data

The oral median lethal dose (LD_{50}) for diazinon in rats ranged from 300 to greater than 2150 mg/kg bw, whereas the dermal LD_{50} was greater than 2000 mg/kg bw. The inhalation median lethal concentration (LC_{50}) was 3.1 mg/L in rats. Diazinon produced mild skin and eye irritation in rabbits. It caused skin sensitization in the guinea-pig Magnusson and Kligman maximization test.

The most sensitive end-point observed in all species given single and repeated doses of diazinon was inhibition of cholinesterase activity. Brain acetylcholinesterase activity was generally decreased at doses higher than those that inhibited erythrocyte acetylcholinesterase activity. Clinical signs of cholinergic toxicity occurred at doses causing more than 50% inhibition of brain acetylcholinesterase activity. Female rats were more sensitive than male rats.

Many repeated-dose toxicity studies are available. In both rats and dogs, no effects other than those related to cholinesterase inhibition have been observed at the lowest-observed-adverse-effect level (LOAEL); in general, effects observed at the highest doses can be considered secondary to the cholinergic toxicity. In these studies, NOAELs ranged from 0.02 to 0.5 mg/kg bw per day, and LOAELs ranged from 1 to 15 mg/kg bw per day, based on erythrocyte acetylcholinesterase inhibition (i.e. > 20%), with brain acetylcholinesterase inhibition (i.e. > 10%) generally appearing at the next higher dose and clinical cholinergic signs appearing at doses above 23 mg/kg bw per day.

In a 28-day acetylcholinesterase inhibition study, rats received diazinon by dietary administration at a concentration of 0, 0.3, 30, 300 or 3000 parts per million (ppm) (equal to 0, 0.02, 2.3, 23 and 213 mg/kg bw per day for males and 0, 0.02, 2.4, 23 and 210 mg/kg bw per day for females, respectively). The NOAEL was 0.3 ppm (equal to 0.02 mg/kg bw per day), on the basis of inhibition of erythrocyte acetylcholinesterase activity at 30 ppm (equal to 2.3 mg/kg bw per day).

In a short-term toxicity study, rats were fed diazinon at a concentration of 0 or 2 ppm (equivalent to 0 and 0.2 mg/kg bw per day, respectively) for 7 days or at a concentration of 0 or 25 ppm (equivalent to 0 and 2.5 mg/kg bw per day, respectively) for 30 days. The NOAEL was 2 ppm (equivalent to 0.2 mg/kg bw per day), based on inhibition of erythrocyte acetylcholinesterase activity at 25 ppm (equivalent to 2.5 mg/kg bw per day).

In a 3-month toxicity study, rats were given diets containing diazinon at a concentration of 0, 0.5, 5, 250 or 2500 ppm (equal to 0, 0.03, 0.3, 15 and 168 mg/kg bw per day for males and 0, 0.04, 0.4, 19 and 212 mg/kg bw per day for females, respectively). The NOAEL was 5 ppm (equal to 0.3 mg/kg bw per day), on the basis of inhibition of erythrocyte and brain acetylcholinesterase activities at 250 ppm (equal to 15 mg/kg bw per day).

In a second 3-month toxicity study, rats were fed diets containing diazinon at a concentration of 0, 0.3, 30, 300 or 3000 ppm (equal to 0, 0.017, 1.7, 17 and 177 mg/kg bw per day for males and 0, 0.019, 1.9, 19 and 196 mg/kg bw per day for females, respectively). The NOAEL was 0.3 ppm (equal to 0.017 mg/kg bw per day), on the basis of inhibition of erythrocyte acetylcholinesterase activity at 30 ppm (equal to 1.7 mg/kg bw per day).

In a third 3-month toxicity study, female rats were fed diets containing diazinon at a concentration of 0, 5, 10 or 15 ppm (equivalent to 0, 0.5, 1 and 1.5 mg/kg bw per day, respectively) for 92 days. In the second phase, female rats were fed diets containing diazinon at a concentration of 0, 1, 2, 3 or 4 ppm (equivalent to 0, 0.1, 0.2, 0.3 and 0.4 mg/kg bw per day, respectively) for 42 days. In the third phase, female rats were fed diets containing diazinon at a concentration of 0, 0.1, 0.5, 1 or 2 ppm (equivalent to 0, 0.01, 0.05, 0.1 and 0.2 mg/kg bw per day, respectively) for 35 days. The NOAEL in the first phase was 5 ppm (equivalent to 0.5 mg/kg bw per day), based on inhibition of erythrocyte acetylcholinesterase activity at 10 ppm (equivalent to 1 mg/kg bw per day) after dosing for 92 days. The NOAEL for females in the second and third phases were the highest tested doses of 4 ppm (equivalent to 0.4 mg/kg bw per day) and 2 ppm (equivalent to 0.2 mg/kg bw per day) after dosing for 42 and 35 days, respectively.

In a fourth 3-month toxicity study, rats were fed diets containing diazinon at a concentration of 0, 5, 125 or 2000 ppm (equal to 0, 0.3, 7.8 and 198 mg/kg bw per day for males and 0, 0.3, 8.9 and 247 mg/kg bw per day for females, respectively). The NOAEL was 5 ppm (equal to 0.3 mg/kg bw per day), on the basis of inhibition of erythrocyte acetylcholinesterase activity at 125 ppm (equal to 7.8 mg/kg bw per day).

In a 90-day repeated-dose neurotoxicity study, rats were dosed in the diet at 0, 25, 125 or 1000 ppm (equal to 0, 1.7, 8.4 and 69.1 mg/kg bw per day for males and 0, 1.8, 9.3 and 82.4 mg/kg bw per day for females, respectively). A NOAEL could not be identified, as erythrocyte acetylcholinesterase activity was inhibited at 1.7 mg/kg bw per day, the lowest dose tested.

In considering the NOAELs and LOAELs identified in the 28-day and 3-month (neuro)toxicity studies in rats measuring the inhibition of acetylcholinesterase activity, the Meeting concluded that the extent of acetylcholinesterase inhibition was not dependent on duration of dosing once steady state had been achieved (within 4 weeks). The overall NOAEL for the 28-day and 3-month (neuro)toxicity studies in rats was 5 ppm, based on inhibition of erythrocyte acetylcholinesterase activity at the overall LOAEL of 10 ppm. In studies where feed consumption data were used to calculate test substance intake, 5 ppm was equal to 0.3 mg/kg bw per day. These substance intake data are considered to be more accurate than those calculated using a default conversion factor, in which the NOAEL of 5 ppm is equivalent to 0.5 mg/kg bw per day.

In a 90-day toxicity study, dogs were given diets containing diazinon at a concentration of 0, 0.1, 0.5, 150 or 300 ppm (equal to 0, 0.0034, 0.020, 5.9 and 10.9 mg/kg bw per day for males and 0, 0.0037, 0.021, 5.6 and 11.6 mg/kg bw per day for females, respectively). The NOAEL was 0.5 ppm (equal to 0.020 mg/kg bw per day), on the basis of inhibition of erythrocyte and brain acetylcholinesterase activities at a dietary concentration of 150 ppm (equal to 5.6 mg/kg bw per day).

In a second 90-day toxicity study, dogs were given diazinon at 0, 0.3, 3 or 10 mg/kg bw per day by gelatine capsule. The NOAEL was 0.3 mg/kg bw per day, on the basis of inhibition of erythrocyte and brain acetylcholinesterase activities at 3 mg/kg bw per day.

In a 1-year toxicity study in dogs given diazinon in the diet at a concentration of 0, 0.1, 0.5, 150 or 300 ppm (equal to 0, 0.0032, 0.015, 4.7 and 7.7 mg/kg bw per day for males and 0, 0.0037, 0.020, 4.5 and 9.1 mg/kg bw per day for females, respectively), the NOAEL was 0.5 ppm (equal to 0.015 mg/kg bw per day), on the basis of inhibition of erythrocyte (males and females) and brain (females only) acetylcholinesterase activities at 150 ppm (equal to 4.5 mg/kg bw per day).

The overall NOAEL for the 90-day and 1-year toxicity studies in dogs was 0.3 mg/kg bw per day, based on inhibition of erythrocyte and brain acetylcholinesterase activities at 3 mg/kg bw per day.

In a pre-GLP carcinogenicity study in mice that was considered adequate to evaluate carcinogenicity but not chronic toxicity, diazinon was administered at a dietary concentration of 0, 100 or 200 ppm (equivalent to 0, 15 and 30 mg/kg bw per day, respectively) over 103 weeks. No treatment-related tumours were observed.

In another pre-GLP carcinogenicity study in mice, diazinon was administered at a dietary concentration of 0, 100, 200, 300 (males) or 400 (females) ppm (equal to 0, 16, 31 and 46 mg/kg bw per day for males and 0, 22, 43 and 86 mg/kg bw per day for females, respectively) for 104 weeks. Cholinesterase activity was not measured in this study. The NOAEL for chronic toxicity was 200 ppm (equal to 31 mg/kg bw per day), based on depression of body weight and lower feed consumption at 300 ppm (equal to 46 mg/kg bw per day). No treatment-related tumours were observed.

In a pre-GLP carcinogenicity study in rats that was considered adequate to evaluate carcinogenicity but not chronic toxicity, diazinon was administered at a dietary concentration of 0, 400 or 800 ppm (equivalent to 0, 20 and 40 mg/kg bw per day, respectively) over 103 weeks. No treatment-related tumours were observed.

In a chronic toxicity study, rats received diazinon in the diet at a concentration of 0 (untreated and vehicle controls), 0.1, 1.5, 125 or 250 ppm (equal to 0, 0.004, 0.06, 5 and 10 mg/kg bw per day for males and 0, 0.005, 0.07, 6 and 12 mg/kg bw per day for females, respectively) for 98/99 weeks. The NOAEL was 1.5 ppm (equal to 0.06 mg/kg bw per day), on the basis of inhibition of erythrocyte and brain acetylcholinesterase activities at 125 ppm (equal to 5 mg/kg bw per day). From the available data, there was no evidence of a tumorigenic response; however, the group size (N = 20) was too small to allow a conclusion to be reached on carcinogenicity.

In a combined chronic toxicity and carcinogenicity study in rats, diazinon was fed in the diet at concentrations adjusted to achieve target concentrations of 0, 0.025, 0.1, 1.5 and 22.5 mg/kg bw per day for 104 weeks. The NOAEL for long-term toxicity was 0.1 mg/kg bw per day, based on inhibition of erythrocyte acetylcholinesterase activity at 1.5 mg/kg bw per day. No treatment-related tumours were observed.

The overall NOAEL for chronic toxicity in rats was 0.1 mg/kg bw per day, based on inhibition of erythrocyte acetylcholinesterase activity at 1.5 mg/kg bw per day.

The Meeting concluded that diazinon is not carcinogenic in mice or rats.

Given the similarity of the sensitivities of mammalian species, an overall NOAEL in all studies of repeated-dose (neuro)toxicity in rats and dogs could be identified. The overall NOAEL was 0.3 mg/kg bw per day, on the basis of inhibition of acetylcholinesterase activity in erythrocytes at 1 mg/kg bw per day.

In studies submitted by the sponsors, diazinon was tested for genotoxicity in an adequate range of assays, both in vitro and in vivo. In addition, many studies with diazinon were described in the published literature, but most of these were considered by the Meeting as inappropriate to evaluate the genotoxicity of diazinon, as they had major deficiencies in study design or reliability (e.g. lack of statistical analysis, testing of mixtures of diazinon with other chemicals and similarity between negative and positive control values). Overall, these studies provided no convincing evidence of genotoxic effects.

The Meeting concluded that diazinon is unlikely to be genotoxic.

In the multigeneration and developmental toxicity studies, cholinesterase activity was not measured.

In a two-generation study on reproductive toxicity, rats received diazinon in the diet at a concentration of 0, 10, 100 or 500 ppm over the course of two generations (F_0 and F_1). Mean diazinon intakes for the F_0 generation during the premating period were 0, 0.77, 7.48 and 32.85 mg/kg bw per day for males and 0, 0.77, 7.48 and 40.26 mg/kg bw per day for females, respectively. The NOAEL for reproductive effects was 100 ppm (equal to 7.48 mg/kg bw per day), based on prolonged gestation duration, decrease in the number of pregnancies, and reduced fertility and mating indices at 500 ppm (equal to 32.85 mg/kg bw per day). The NOAEL for parental effects was 10 ppm (equal to 0.77 mg/kg bw per day), based on reduced parental body weight gain at 100 ppm (equal to 7.48 mg/kg bw per day). The NOAEL for offspring toxicity was 10 ppm (equal to 0.77 mg/kg bw per day), based on reduced viability of pups and pup weights at 100 ppm (equal to 7.48 mg/kg bw per day).

In another two-generation study on reproductive toxicity, rats received diazinon in the diet at a concentration of 0, 0.1, 1.0 or 10 mg/kg (equivalent to 0, 0.0067, 0.067 and 0.67 mg/kg bw per day, assuming concentrations are in mg/kg feed or ppm) over the course of two generations (F_0 and F_1). A rationale for the dose selection was not provided. There were no treatment-related effects observed in F_0 or F_1 parental animals or pups. The NOAEL for reproductive, parental and offspring toxicity was 10 ppm (equivalent to 0.67 mg/kg bw per day), the highest dose tested.

In a range of studies on estrogenic and androgenic activities, no estrogenic, androgenic or anti-androgenic activity was observed at concentrations relevant to human exposure via the diet.

Overall NOAELs from the multigeneration studies in rats were identified. The overall NOAEL for reproductive effects was 100 ppm (equal to 7.48 mg/kg bw per day), based on effects at 500 ppm (equal to 32.85 mg/kg bw per day). The overall NOAEL for parental toxicity was 10 ppm (equal to 0.77 mg/kg bw per day), based on effects at 100 ppm (equal to 7.48 mg/kg bw per day). The overall NOAEL for offspring toxicity was 10 ppm (equal to 0.77 mg/kg bw per day), based on effects at 100 ppm (equal to 7.48 mg/kg bw per day).

In a study of developmental toxicity evaluated by the 1993 JMPR, rats were administered diazinon via gavage at a dose of 0, 15, 50 or 100 mg/kg bw per day. A marked decrease in maternal feed consumption correlating with weight loss at the beginning of the treatment period and a slightly higher incidence of incomplete ossification at different sites in the fetuses were observed at 100 mg/kg bw per day. As limited information was available from the previous JMPR monograph, the Meeting was unable to identify a NOAEL for this study.

In a study of developmental toxicity, rats were administered diazinon via gavage at a dose of 0, 10, 20 or 100 mg/kg bw per day. The NOAEL for maternal toxicity was 20 mg/kg bw per day, based on body weight loss on gestation days 6–10, reduced body weight/body weight gains throughout treatment and decreased feed consumption on gestation days 6–9 at 100 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 20 mg/kg bw per day, based on an increased incidence of rudimentary 14th ribs at 100 mg/kg bw per day.

In a study of developmental toxicity, rabbits were dosed with diazinon via gavage at 0, 7, 25 or 100 mg/kg bw per day. The NOAEL for maternal toxicity was 25 mg/kg bw per day, based on mortality, tremors, convulsions, hypoactivity, anorexia and reduced body weight gain observed at 100 mg/kg bw per day. The NOAEL for embryo/fetal toxicity was 100 mg/kg bw per day, the highest dose tested.

In another developmental toxicity study, diazinon was administered to pregnant rabbits by gavage at a dose level of 0, 2.5, 10 or 40 mg/kg bw per day. The NOAEL for maternal toxicity was 10 mg/kg bw per day, based on clinical signs, decreased body weight and reduced feed consumption. The NOAEL for embryo/fetal toxicity was 10 mg/kg bw per day, based on decreased fetal weight at 40 mg/kg bw per day.

The overall NOAEL for maternal toxicity in developmental toxicity studies in rabbits was 25 mg/kg bw per day, based on effects at 40 mg/kg bw per day, and the overall NOAEL for embryo/fetal toxicity was 10 mg/kg bw per day, based on effects at 40 mg/kg bw per day.

The Meeting concluded that diazinon is not teratogenic.

In a limited acute neurotoxicity study in which acetylcholinesterase activity was not measured, rats were dosed with diazinon at 0, 100, 300 or 500 mg/kg bw by gavage. The NOAEL was 100 mg/kg bw, based on systemic toxicity and clinical signs of neurotoxicity observed at 300 or 500 mg/kg bw. In another acute toxicity study, rats were administered a single dose of diazinon by gavage at 0, 2.5, 150, 300 or 600 mg/kg bw. The NOAEL was 2.5 mg/kg bw, on the basis of depressed erythrocyte acetylcholinesterase activity and behavioural changes at 150 mg/kg bw. In a third study, rats were administered a single dose of diazinon by gavage at 100, 250 or 500 mg/kg bw for males or 0, 0.05, 0.12, 0.25, 2.5, 25 or 250 mg/kg bw for females. The NOAEL was 2.5 mg/kg bw, on the basis of inhibition of brain and erythrocyte acetylcholinesterase activities in females at 25 mg/kg bw.

In a study that investigated the time course of acute inhibition of acetylcholinesterase activity, rats were given a single dose of diazinon by gavage at 0, 2.5, 150, 300 or 600 mg/kg bw, and brain and blood samples were collected at 3, 9 and 24 hours after dosing. The NOAEL was 2.5 mg/kg bw, based on inhibition of brain and erythrocyte acetylcholinesterase activities at 150 mg/kg bw. Inhibition was observed beginning at 3 hours post-dosing, with maximal inhibition at 9 hours post-dosing.

The overall NOAEL in all studies of acute toxicity was 2.5 mg/kg bw, on the basis of inhibition of acetylcholinesterase activity in erythrocytes and in the brain at 25 mg/kg bw in rats of both sexes.

Three studies were performed on delayed neurotoxicity in the hen. Oral doses of diazinon technical ranging from 10 to 100 mg/kg bw were administered to hens. Inhibition of cholinesterase activity was observed from 20 mg/kg bw, but there was no evidence that diazinon caused acute delayed neurotoxicity in the hen.

No specific studies on immunotoxicity were submitted. A study in the open literature with intraperitoneal injection of diazinon in mice was not informative. The submitted repeated-dose toxicity studies do not indicate an immunotoxic potential for diazinon after oral exposure.

Toxicological data on metabolites and/or degradates

No toxicological data were available on any metabolites of diazinon other than diazoxon, which is the active metabolite of diazinon. However, the Meeting concluded that none of the other metabolites would be of toxicological concern at the levels present in the diet.

Human data

In a study of acute toxicity in male volunteers given ascending doses of diazinon (seven volunteers per group given 0.03, 0.12, 0.20 or 0.21 mg/kg bw; one volunteer given 0.30 mg/kg bw), acetylcholinesterase activity was not inhibited in erythrocytes at 0.21 mg/kg bw, the second highest dose tested. The highest dose (0.30 mg/kg bw) was not informative, as it was tested in a single volunteer only. Plasma cholinesterase activity was inhibited by more than 20% at doses above 0.12 mg/kg bw.

Repeated-dose studies in four male volunteers given diazinon for 28–37 days showed that, although there was some inhibition of plasma cholinesterase activity at the highest tested dose of 0.03 mg/kg bw per day (actual administered doses varied slightly, i.e. 0.03, 0.027, 0.022/0.027 and 0.026 mg/kg bw per day), no inhibition of erythrocyte acetylcholinesterase activity was observed.

Diazinon was evaluated in four male volunteers who received diazinon in capsules at 0.025 mg/kg bw per day for 37–43 days. There were no consistent treatment-related effects on erythrocyte acetylcholinesterase activity, blood chemistry or urine analysis. No clinical effects were reported. The NOAEL was 0.025 mg/kg bw per day, the only dose tested.

The overall NOAEL from repeated-dose studies in humans was 0.03 mg/kg bw per day.

Several epidemiological studies on cancer outcomes following occupational exposure to diazinon were available. The review of these studies focused on the occurrence of three cancer types: NHL, leukaemia and lung cancer (see section 2.2). One prospective cohort study was available, the Agricultural Health Study (AHS), with a large sample size and detailed exposure assessment. Cohort studies are considered a powerful design, as recall bias is avoided. All other studies were case–control studies, usually retrospective, which are more prone to recall and selection biases.

There was no significant evidence of a positive association of NHL with diazinon exposure and no evidence of an exposure–response relationship in the AHS. In a large pooled case–control study, the unadjusted estimates showed a significant elevated risk of NHL (relative risk [RR] = 1.7; 95% confidence interval [CI] = 1.2–2.5) associated with ever versus never use of diazinon. However, these risks were attenuated and/or no longer significant when proxy respondents were excluded and analyses were mutually adjusted for other pesticides (malathion, fonofos). Although increasing risk across exposure duration categories was observed, which was suggestive of a duration–response pattern, confidence intervals were non-significant, wide and overlapping between categories. Two other studies reported elevated risks of NHL for ever versus never use of diazinon or high versus low

diazinon use, but confidence intervals were wide, reflecting uncertainty in the risk estimates, and chance could not be excluded as an explanation for the findings. Overall, there was no convincing evidence of a positive association between NHL and exposure to diazinon.

A significantly increased risk of leukaemia in the highest exposure category (> 38.8 lifetime days of diazinon exposure; RR = 3.36; 95% CI = 1.08–10.49) and a significant exposure–response relationship were observed in the AHS. Findings for intensity-weighted lifetime exposure days demonstrated a similar pattern, but did not reach significance. Two other studies reported non-significantly elevated risks of leukaemia for high versus low diazinon use and ever versus never use of diazinon, with a non-significant dose–response relationship observed using days of use per year. Overall, there is weak evidence of a positive association between leukaemia and exposure to diazinon from the AHS only. It is noted that the number of diazinon-exposed cases was low or not reported in all three available studies.

A significant 60% excess risk of lung cancer in the highest exposure category (> 38.8 lifetime days of diazinon exposure) and a significant trend across exposure categories were observed in the AHS. Findings for intensity-weighted lifetime exposure days demonstrated a similar pattern, but did not reach significance. A separate analysis of ever use of diazinon versus never use from the AHS found no evidence of elevated risk of lung cancer among spouses of farmers/pesticide applicators; however, there were only 15 exposed cases. One other study reported a non-significant elevated risk of lung cancer for ever versus never use of diazinon (based on 17 exposed cases). Overall, there is weak evidence of a positive association between lung cancer and exposure to diazinon from the AHS cohort study only.

In view of the lack of genotoxicity and the absence of carcinogenicity in mice and rats and considering the available epidemiological data from occupational exposure, the Meeting concluded that diazinon is unlikely to pose a carcinogenic risk to humans via exposure from the diet.

The Meeting concluded that the existing database on diazinon was adequate to characterize the potential hazards to the general population, including fetuses, infants and children.

Toxicological evaluation

The Meeting identified inhibition of acetylcholinesterase activity as the most sensitive end-point after single or repeated doses of diazinon in all species. After considering all previously evaluated data and the new studies, the Meeting established an ADI of 0–0.003 mg/kg bw, based on the overall NOAEL of 0.3 mg/kg bw per day from all repeated-dose toxicity studies, and using a safety factor of 100. This ADI was supported by the NOAEL of 0.03 mg/kg bw per day, the highest dose tested, identified in repeated-dose studies that involved a limited number of male volunteers, with application of a safety factor of 10.

In 2006, the Meeting established an ADI of 0–0.005 mg/kg bw, based on the highest NOAEL of 0.5 mg/kg bw per day for inhibition of erythrocyte acetylcholinesterase activity at 1 mg/kg bw per day in a 92-day repeated-dose toxicity study in rats and using a safety factor of 100. In this study, the dietary concentrations of diazinon were converted to units of milligrams per kilogram body weight per day using a default conversion factor; the present Meeting considers this less reliable than the conversion using feed consumption data.

The Meeting reaffirmed the ARfD of 0.03 mg/kg bw established by the 2006 JMPR. This ARfD was based on the NOAEL of 2.5 mg/kg bw identified in studies of acute (neuro)toxicity in rats, and using a safety factor of 100. This ARfD was supported by the NOAEL of 0.21 mg/kg bw, the highest dose tested, identified in the study in which a limited number of male volunteers were given a single dose of diazinon, with application of a safety factor of 10.

A toxicological monograph was prepared.

Levels relevant to risk assessment of diazinon

Species	Study	Effect	NOAEL	LOAEL
Mouse	Two-year study of carcinogenicity[a,b]	Toxicity	200 ppm, equal to 31 mg/kg bw per day	300 ppm, equal to 46 mg/kg bw per day
		Carcinogenicity	300 ppm, equal to 46 mg/kg bw per day[c]	–
Rat	Acute (neuro)toxicity studies[d,e] (acetylcholin-esterase inhibition)	Toxicity	2.5 mg/kg bw	25 mg/kg bw
	Four-week or 3-month studies of (neuro)toxicity[a,e]	Toxicity	5 ppm, equal to 0.3 mg/kg bw per day[f]	10 ppm, equivalent to 1 mg/kg bw per day
	Two-year studies of toxicity and carcinogenicity[a,e]	Toxicity	0.1 mg/kg bw per day[f]	1.5 mg/kg bw per day
		Carcinogenicity	800 ppm, equivalent to 40 mg/kg bw per day[c]	–
	Two-generation studies of reproductive toxicity[a,b,e]	Reproductive toxicity	100 ppm, equal to 7.48 mg/kg bw per day	500 ppm, equal to 32.85 mg/kg bw per day
		Parental toxicity	10 ppm, equal to 0.77 mg/kg bw per day	100 ppm, equal to 7.48 mg/kg bw per day
		Offspring toxicity	10 ppm, equal to 0.77 mg/kg bw per day	100 ppm, equal to 7.48 mg/kg bw per day
	Developmental toxicity study[b,d]	Maternal toxicity	20 mg/kg bw per day	100 mg/kg bw per day
		Embryo and fetal toxicity	20 mg/kg bw per day	100 mg/kg bw per day
Rabbit	Developmental toxicity studies[b,d,e]	Maternal toxicity	25 mg/kg bw per day	40 mg/kg bw per day
		Embryo and fetal toxicity	10 mg/kg bw per day	40 mg/kg bw per day
Dog	Ninety-day and 1-year studies of toxicity[a,e]	Toxicity	0.3 mg/kg bw per day[f]	3 mg/kg bw per day
Rat, dog	Repeat-dose (neuro)toxicity studies[e]	Toxicity	5 ppm, equal to 0.3 mg/kg bw per day	10 ppm, equivalent to 1 mg/kg bw per day
Human	Acute toxicity study[d]	Toxicity	0.21 mg/kg bw[c]	–
	Four/five-week studies of toxicity[d,e]	Toxicity	0.03 mg/kg bw per day[c]	–

[a] Dietary administration.
[b] Acetylcholinesterase activity not measured.
[c] Highest dose tested.
[d] Gavage administration.
[e] Two or more studies combined.
[f] Included in the overall NOAEL for rats and dogs.

Estimate of acceptable daily intake (ADI)

0–0.003 mg/kg bw

Estimate of acute reference dose (ARfD)

0.03 mg/kg bw

Information that would be useful for the continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposure

Critical end-points for setting guidance values for exposure to diazinon

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Nearly complete and rapid (~90% at 10 mg/kg bw within 24 h)
Dermal absorption	No data
Distribution	Widely distributed at low concentrations
Potential for accumulation	No potential for accumulation
Rate and extent of excretion	Predominantly in urine (86–93% at 10 mg/kg bw within 24 h)
Metabolism in animals	Rapidly degraded to diazoxon and subsequently mainly via oxidase/hydrolase-mediated cleavage of the ester bond, and further oxidation at the isopropyl substituent to yield hydroxy pyrimidinols
Toxicologically significant compounds in animals and plants	Parent compound and diazoxon
Acute toxicity	
Rat, LD_{50}, oral	300 to > 2 150 mg/kg bw
Rat, LD_{50}, dermal	> 2 000 mg/kg bw
Rat, LC_{50}, inhalation	3.1 mg/L
Rabbit, dermal irritation	Mildly irritating
Rabbit, ocular irritation	Mildly irritating
Guinea-pig, dermal sensitization	Sensitizing (Magnusson and Kligman maximization test)
Repeat-dose studies of (neuro)toxicity	
Target/critical effect	Acetylcholinesterase inhibition
Overall oral NOAEL	0.3 mg/kg bw per day (rat, dog)
Lowest relevant dermal NOAEL	3 mg/kg bw per day (21 days; rat)
Lowest relevant inhalation NOAEC	0.46 mg/m^3 (21 days; rat)
Long-term studies of carcinogenicity	
Carcinogenicity	Not carcinogenic in mice or rats[a]
Genotoxicity	
	No evidence of genotoxicity by the oral route[a]

Reproductive toxicity	
Target/critical effect	Mortality, reduced parental body weight gain, reduced viability of pups and pup weights, prolonged gestation duration, decrease in number of pregnancies, and reduced fertility and mating indices
Lowest relevant parental NOAEL	0.77 mg/kg bw per day (rat)
Lowest relevant offspring NOAEL	0.77 mg/kg bw per day (rat)
Lowest relevant reproductive NOAEL	7.48 mg/kg bw per day (rat)
Developmental toxicity	
Target/critical effect	Clinical signs, reduced maternal body weight and feed consumption, and reduced fetal weight
Lowest relevant maternal NOAEL	25 mg/kg bw per day (rabbit)
Lowest relevant embryo/fetal NOAEL	10 mg/kg bw per day (rabbit)
Neurotoxicity[b]	
Acute neurotoxicity NOAEL	2.5 mg/kg bw (acetylcholinesterase inhibition; rat)
Developmental neurotoxicity NOAEL	No data
Acute delayed neurotoxicity	No evidence (hens)
Human data	Acetylcholinesterase inhibition:
	Acute toxicity NOAEL: 0.21 mg/kg bw, highest dose tested
	Subchronic toxicity NOAEL: 0.03 mg/kg bw per day, highest dose tested (4/5 weeks)

[a] Unlikely to pose a carcinogenic risk to humans via exposure from the diet.
[b] Ninety-day neurotoxicity study in rats is covered by the overall NOAEL for repeated-dose studies of (neuro)toxicity.

Summary

	Value	Study	Safety factor
ADI	0–0.003 mg/kg bw	Repeated-dose toxicity studies (rat, dog)	100
ARfD	0.03 mg/kg bw	Acute (neuro)toxicity studies (rat)	100

DIETARY RISK ASSESSMENT

Long-term dietary exposure

The ADI for diazinon is 0–0.003 mg/kg bw. The international estimated daily intakes (IEDIs) for diazinon were estimated for the 17 Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) cluster diets using the supervised trials median residue (STMR) or STMR in a processed commodity (STMR-P) values estimated by the 1996 (animal commodities), 1999 (pome fruit, cabbage head) and 2006 (cranberries) JMPRs. An STMR value for tomato was estimated using the data reported in the 1993 JMPR evaluation monograph. For all other commodities, the maximum residue limits (MRLs) were used, as STMR values were not available. The results are shown in Annex 3. The IEDI ranged from 3% to 50% of the

maximum ADI. The Meeting concluded that the long-term dietary exposure to residues of diazinon from uses that have been considered by JMPR is unlikely to present a public health concern.

Short-term dietary exposure

The ARfD for diazinon is 0.03 mg/kg bw. The international estimate of short-term dietary intake (IESTI) was calculated. The calculation employed highest residue (HR) values where these could be identified in the relevant JMPR reports; otherwise, the MRL was used. In the case of meat, the Meeting noted that residues in fat are approximately 15 times higher than those in muscle and used the MRL value of 2 mg/kg for fat and 0.1333 mg/kg for muscle. The results are shown in Annex 4. The IESTI represented a maximum of 100% of the ARfD for both children and the general population. The Meeting concluded that the short-term dietary exposure to diazinon residues from uses considered by JMPR was unlikely to present a public health concern.