METHYL PARATHION

This is a compilation of abstracts of articles identified during the preliminary toxicological evaluation of evidence on the developmental and reproductive toxicity for methyl parathion (parathion-methyl, dimethyl parathion, CAS#298-00-0). Methyl parathion is a regulated insecticide with restricted uses with restricted uses limited to licensed applicators.

The abstracts compiled below are from animal toxicity and epidemiologic studies reporting on developmental and reproductive sequelae related to exposure to methyl parathion, as well as other relevant investigations (e.g., *in vitro* studies or studies in non-mammalian animal species). This information was used to screen chemicals to propose for listing consideration by the Developmental and Reproductive Toxicant Identification Committee. The criteria for passing the current screen are the existence of the following number of reports of an increase in adverse developmental or reproductive toxicity outcomes in mammalian species:

1) a total of 15 or more reports across all of the endpoints (developmental toxicity,female reproductive toxicity, male reproductive toxicity) or
2) 10 or more reports for any one category of the following three categories: developmental toxicity, female reproductive toxicity, or male reproductive toxicity.

There were a total of 127 studies identified in the literature search on methyl parathion (some studies may have reported more than one adverse effect). The table below shows how methyl parathion passed the screen.

Endpoints	Reports of adverse effects		Reports of no adverse effects	
	Animal	Human	Animal	Human
Developmental	5	0	0	0
Female reproductive	7	0	0	0
Male reproductive	9	2	0	0
Total	21	2	0	0

In addition to the reports enumerated in the table, the search identified:

- 2 related studies or meeting presentations (titles of reports only provided below)
- 65 studies with information relevant to the reproductive and/or developmental toxicity of methyl parathion in wildlife or other non-rodent or rabbit test species (with or without abstracts)
- 14 studies with related information, but no direct data on reproductive or developmental toxicity
- 20 publications with a relevant title but no abstract

- Studies for which a "Summary of Toxicology Data" was produced by staff of the Department of Pesticide Regulation (DPR) of the California Environmental Protection Agency. These summaries of full data sets on teratology and reproductive toxicology studies submitted for regulatory purposes are provided below as well. Boldfaced and capitalized words appear exactly as in the original DPR summaries.

Contents Page

I. Animal Developmental and Reproductive Toxicity Studies …… 4

A. Studies reporting developmental or reproductive toxicity …… 4

i. Developmental toxicity…… 4

a. Studies identified in the open literature search ……... 4

b. Studies with DPR Tox Summaries that have developmental endpoints…… 6

ii. Female reproductive toxicity…… 9

a. Studies identified in the open literature search ……... 9

b. Studies with DPR Tox Summaries that have female reproductive endpoints…… 12

iii. Male reproductive toxicity……..... 16

a. Studies identified in the open literature search …….. 16

B. Studies reporting no developmental or reproductive toxicity…….. 22

II. Epidemiologic Developmental and Reproductive Toxicity Studies…… 22

A. Studies reporting increased risk of adverse developmental or reproductive outcomes……..…. 22

i. Developmental toxicity…… ….. 22

ii. Female reproductive toxicity……..…. 22

iii. Male reproductive toxicity……..… 22

B. Studies reporting no increased risk of adverse developmental or reproductive outcomes…… 23

III. Other Relevant Information…….. 24

A. Meeting Abstracts …….. 24

B. Related articles …..... 24

C. Publications with a relevant title but no abstract ……..…….…..... 30

I. Animal Developmental and Reproductive Toxicity Studies

A. Studies reporting developmental or reproductive toxicity

i. Developmental toxicity

a. Studies identified in the open literature search

Methyl parathion induced teratological study in rats.
Sunil Kumar K. B. and Devi K. S.
J Environ Biol. 1996;17(1):51-7.

Pregnant rats received daily P.O. doses of organophosphate methyl parathion (MP) from day 6 through day 15 of gestation at doses 0.5, 1 and 1.5 mg/kg body weight. Dams were sacrificed on day 20 of gestation and fetuses were examined for external and visceral anomalies. Significant decrease in dam weight gain during pregnancy and increase in resorption rate were observed in 1.5 mg MP administered rats. No increase were seen in skeletal or visceral anomalies in treatment groups, however an increase in incidence of haemorrhagic spots in brain and upper body were seen in pups from dams treated with MP.

Brain cholinergic, behavioral, and morphological development in rats exposed in utero to methylparathion.
Gupta R. C., Rech R. H., Lovell K. L., Welsch F. and Thornburg J. E..
Toxicol Appl Pharmacol. 1985, Mar 15; 77(3):405-13.

The purpose of this study was to determine the effects of subchronic administration of the organophosphate methylparathion (MPTH) during gestation on behavior and development of brain cholinergic neurons in the offspring. Pregnant rats received daily po doses of MPTH from Day 6 through Day 20 of gestation at doses causing no (1.0 mg/kg) or minimal (1.5 mg/kg) visible signs of maternal toxicity. Acetylcholinesterase (AChE) and choline acetyltransferase (CAT) activities, and [3H]quinuclidinyl benzilate (QNB) binding to muscarinic receptors, were determined in several brain regions at 1, 7, 14, 21, and 28 days postnatal age and in maternal brain at Day 19 of gestation. Prenatal exposure to 1.5 mg MPTH/kg reduced AChE and increased CAT activity in all brain regions at each developmental period and in maternal brain. Similar exposure to 1.0 mg MPTH/kg caused a significant but smaller and less persistent reduction in AChE activity but no change in brain CAT activity of the offspring. Both doses of MPTH decreased the Bmax of 3H-QNB binding in maternal frontal cortex but did not alter the postnatal pattern of 3H-QNB binding. In parallel studies, prenatal exposure to MPTH did not affect a variety of behaviors. However, cage emergence, accommodated locomotor activity, and operant behavior in a mixed paradigm were impaired in rats exposed to 1.0 but not to 1.5 mg/kg MPTH. No morphological changes were observed in hippocampal or cerebellar tissue. Thus, subchronic prenatal exposure to MPTH altered postnatal development of cholinergic neurons and caused subtle alterations in selected behaviors

of the offspring.

Effect of subchronic administration of methyl parathion on in vivo protein synthesis in pregnant rats and their conceptuses.
Gupta R. C., Thornburg J. E., Stedman D. B. and Welsch F..
Toxicol Appl Pharmacol. 1984, Mar 15; 72(3):457-68.

Pregnant rats received daily po doses of the organophosphate methyl parathion (MPTH) from Day 6 through Day 15 or 19 of gestation at doses causing no (1.0 mg/kg) or minimal (1.5 mg/kg) signs of maternal toxicity. Following the dose of MPTH on Day 15 or 19, in vivo protein synthesis was measured 0.5, 1.0, and 2.0 hr after sc injection of L-[1-14C]valine at a dose of 5 microCi/mmol/100 g body wt. The specific activity of [14C]valine in the free amino acid pool and protein bound pool was significantly reduced in various regions of maternal brain and in maternal viscera, placenta, and whole embryos (Day 15), and in fetal brain and viscera (Day 19). The inhibitory effect of MPTH on net protein synthesis was dose dependent, greater on Day 19 than 15 of gestation and more pronounced in fetal than in maternal tissues.

Behavioral effects of methyl parathion and toxaphene exposure in rats.
Crowder L. A., Lanzaro G. C. and Whitson R. S.
J Environ Sci Health B. 1980;15(4):365-78.

The behavior of rats exposed peri- and postnatally to methyl parathion (MP) and toxaphene (T) was examined with a variety of maturational and learning tests. Females received daily oral doses of 1.0 mg/kg MP or 1.0 mg/kg MP + 2.0 mg/kg T between Days 7-15 of pregnancy. With T alone, rats of the postnatal group were dosed daily with 6 mg/kg for 21 days, while in the perinatal study females received 6 mg/kg daily from Day 7 of pregnancy until parturition. Rat pups exposed to sublethal doses of MP and T in combination or alone demonstrated few significant changes in learning ability as measured by a simple two-choice maze, motor skills, or behavior.

[Studies on the prenatally toxic effect of parathionemethyl in Wistar rats compared to cyclophosphamide and trypan blue].
Fuchs V., Golbs S., Kuehnert, M. and Osswald F.
Arch Exp Veterinarmed. 1976;30(3):343-50.

Higher yield and performance in plant and animal production will depend on reinforced use of pesticides, particularly alkyl phosphate esters and insecticidal carbamates. Prenatal toxic action of the pesticides used today may be detrimental to human and animal health. Prenatal-toxicological tests, using parathion-methyl, were conducted on the basis of known but modified experimental methods. The vulnerability of a rat strain was tested by applying to it teratogenic model substances (trypan blue and cyclophosphamide). Several oral applications of parathion-methyl (3 ppm) during the sensitive phases of germ formation and growth (fifth to ninth and eleventh to fifteenth or eleventh to nineteenth days from conception) were followed by clear embryotoxic

effects, such as retardation and increased resorption. The average number of resorption sites grew from nine in the control group to 20 in the experimental group. Postnatal malformations were not observed.

b. Studies with DPR Tox Summaries that have developmental endpoints

Two-Generation Reproductive Study of Methyl Parathion in Rats
Bio/dynamics, Report No. BD-80-139, 7/18/82
(as summarized by California Department by Pesticide Regulation)

Methyl parathion, 93.6% pure, was given in the diet to Sprague- Dawley CD rats (15 males & 30 females/group) at 0 (acetone = vehicle), 0.5, 5.0 and 25 ppm for two generations (one litter/generation). Maternal NOEL = 5 ppm (marginal decrease in weight gain at the end of lactation); Maternal NOAEL > 25 ppm; Reproductive NOEL and NOAEL = 5 ppm (decreased pup survivability). Formerly reviewed as unacceptable (Schreider, 3/18/85) for no justification of dose levels, no characterization of test article, no litter standardization, and incomplete histopathology. The study was upgraded to ACCEPTABLE based on an EPA Memorandum resulting in a re-review of the study. Another reevaluation of the study, prompted by the rebuttal in Record No. 086795, resulted in the decreased pup survivability being identified as a POSSIBLE ADVERSE HEALTH EFFECT. EPA One liner: Core Grade Minimum.

Three-Generation Reproductive Study of Methyl Parathion in Rats
Bayer, Report No. 053 037190,12/8/82
(as summarized by California Department by Pesticide Regulation)

Methyl parathion (95%) was given in the diet at 0, *2,* 10 and 50 ppm for a three generation study; 10 males/group, 20 females/group. There were no pups surviving at the end of F2 generation in the high dose group; NOEL = 2 ppm; UNACCEPTABLE (needs QA statement and final report revisions, no analysis of diet for test article, food consumption not measured, no clinical observations. presented, incomplete necropsy data, gestation and lactation weights included in weekly female weights), NOT UPGRADEABLE.

Three-Generation Reproductive Study of Methyl Parathion in Rats
P.M. Dolinger Assoc., Report No. 033 927643, 1979
(as summarized by California Department by Pesticide Regulation)

Summary of 3-generation study using methyl parathion (10 and 30 ppm in the diet) conducted by Woodard Research Corp. Reductions in survival noted for Fla, F1b, and F2a generations at 30 ppm and in the F-3a generation at 10 ppm; stillbirth rates were increased in F1b and F3b generations at 30 ppm; UNACCEPTABLE (no data), NOT UPGRADEABLE. EPA One liner: Core Grade Supplementary.
SUMMARY: A consistent finding in the three rat reproduction studies on file was a decrease in pup survivability. In two of the studies (#Is 927643 and 037190) where the

doses included 0, *2,* 10, 30 and 50 ppm, decreased survivability was observed at 10 ppm. In the third study (#011171) where the doses were 0, 0.5, 5.0, and 25 ppm, survivability was decreased at 25 ppm. Taken together, these data indicate decreased pup survivability is a consistent possible adverse effect with a NOEL = 5 ppm.

Teratology Study of Methyl Parathion in Rats
Research and Consulting Company AG, RCC 083553, 12/31/87
(as summarized by California Department by Pesticide Regulation)
Technical methyl parathion, batch 230 606 003, 97% pure in 0.5% aqueous Cremophor EL was administered by oral intubation to groups of 25 mated Wistar/HAN female rats at 0 (vehicle control), 0.3, 1.0 and 3.0 mg/kg/day on days 6 through 15 of gestation. An additional 10 females each were added to the 0 and 3.0 mg/kg/day groups for cholinesterase activity measurement. **Possible adverse effects:** Decreased maternal cholinesterase activity, maternal signs of organophosphate toxicity, decreased maternal weight gain, decreased maternal food consumption, fetal developmental delay determined by decreased fetal weight and delayed ossification, and a tendency toward increased resorptions, all at 3.0 mg/kg/day. Maternal NOEL = 1.0 mg/kg/day (signs of organophosphate toxicity, cholinesterase inhibition, decreased food consumption and weight gain). Developmental NOEL = 1.0 mg/kg/day (developmental delay and marginal increase in resorptions). ACCEPTABLE study.

Teratology Study of Methyl Parathion in Rats
Bayer, 055 037196, 6/3/77
(as summarized by California Department by Pesticide Regulation)

Methyl parathion (94.4%) by oral gavage at 0, 0.1, 0.3 and 1.0 on days 6-15 of gestation; 20 pregnant females/group; fetal body weight decreased in high dose group; NOEL cannot be determined; UNACCEPTABLE (need analysis of dosing solution; need individual data for body weight, food consumption, necropsy parameters, fetal exams, fetal weights and clinical observations.), POSSIBLY UPGRADEABLE.. EPA One liner: Core Grade Supplementary.

Teratology Study of Methyl Parathion in Rats
Dolinger Assoc, 033 038392
(as summarized by California Department by Pesticide Regulation)

Summary of journal article by Fish (1966) in which rats were injected i.p. with methyl parathion on day 9 or 15 of gestation; insufficient data for evaluation. Study by Tanimura et al. (1967) suggests that one i.p. injection of methyl parathion at 15 mg/kg on day 12 of gestation reduced fetal weight. EPA One liner: Core Grade Supplementary.

Teratology Study of Methyl Parathion in Rabbits
Argus Research Laboratories, 095 111287, 11/16/91
(as summarized by California Department by Pesticide Regulation)

Methyl parathion technical (95.7% pure) was administered by gavage to artificially inseminated New Zealand White [Hra:(NZW)SPF] female rabbits (19 or 20/group) on gestation days 6 through 18 at 0 (corn oil), 0.3, 3.0, and 9.0 mg/kg/day. Maternal cholinesterase NOEL < 0.3 mg/kg/day (Significant RBC Cholinesterase inhibition occurred at > 3.0 mg/kg/day. A significant decrease in plasma Cholinesterase occurred at 9.0 mg/kg/day. Maternal Systemic NOEL: There were no significant maternal effects at any dose. Developmental NOEL = 3.0 mg/kg/day (There was an increased incidence in thickened areas of ossification in the ribs at 9.0 mg/kg/day). **Acceptable, with no adverse effects**.

Teratology Study of Methyl Parathion in Rabbits
Bayer AG, 055 037197, 9/4/84
(as summarized by California Department by Pesticide Regulation)

Methyl parathion, 95.7% pure in 0.5% aqueous Cremophor EL emulsion vehicle was administered by oral gavage to groups of 12-15 pregnant Himalayan CHBB:HM rabbits at 0 (vehicle control), 0.3, 1.0 and 3.0 mg/kg/day on days 6-18 of gestation. No adverse effects were noted. Maternal and Developmental NOEL > 3 mg/kg/day. Initially reviewed as unacceptable but possibly upgradeable with submission of justification of dosing levels, all the individual animal data, a description of the dosing solution preparation, and an analysis of the dosing solution (Parker, 12/4/85). After review of the supplemental information provided in record nos. 085035 and 088518, the study remains UNACCEPTABLE and is now considered not upgradeable due to the lack of a MTD. EPA One liner: Core Grade Minimum

Teratology Study of Methyl Parathion in Rabbits (supplement)
Bayer, 068 085035, 12/22/87
(as summarized by California Department by Pesticide Regulation)

Supplemental to record no. 037197, consisting of a retrospective range finding study in rabbits at doses of 0, 0.3, 1.0, and 3.0 mg/kg/day. The only notable finding was a minimal reduction in RBC cholinesterase activity on days 14 and 19 in the high dose group.

Teratology Study of Methyl Parathion in Rabbits (supplement)
Bayer AG, 083 088518, 12/22/87
(as summarized by California Department by Pesticide Regulation)

Supplemental to record no. 037197, consisting of a dose justification based on a rat teratology study, individual animal data, test compound analysis, and an abbreviated study protocol (G. Chernoff, 7/2/90). NOTE: Justification for the dose selection used in

the rabbit teratology study (DPR Record No. 037197) has been provided in two separate documents. In the first (DPR Record No. 085035), the results of a retrospective range-finding study were presented. The only finding indicative of an MTD was a marginal decrease in RBC cholinesterase levels at 3.0 mg/kg/day, the highest dose tested. Plasma and brain cholinesterase levels were unaffected by the treatment, as were appearance, behavior, weight gain, autopsy findings, and maternal deaths. The second justification (DPR Record No. 088518), was based on the results of an unacceptable rat teratology study (DPR Record No. 037196), in which a maternal MTD was not clearly established. These data for the rat study are considered inadequate, and inappropriate for dose justification in the rabbit study. Since the demonstration of a clear MTD was not achieved in either the original rabbit teratology study, or in the retrospective range finding study, this information is not sufficient to fill the data gap. DPR Record No. 111287 (Argus Research Laboratories, 11/16/91), however, is an acceptable rabbit teratology study and therefore, the data gap is filled.

Teratology Study of Methyl Parathion in Mice
Dolinger Assoc, 033 038392, *(as summarized by California Department by Pesticide Regulation)*

Summary of journal article by Tanimura et al. (1967) in which mice were injected once i.p. with 20 or 60 mg/kg on day 10 of gestation; in high dose group 13 of 112 fetuses had cleft palate, fetal deaths elevated at the high dose level. EPA One liner: Core Grade Supplementary.

ii. Female reproductive toxicity

a. <u>Studies identified in the open literature search</u>

Biochemical effects of some organophosphorus pesticides on the ovaries of albino rats.
Kaur S. and Dhanju C. K.
Indian J Physiol Pharmacol. 2005;49(2):148-52. [Indian journal of physiology and pharmacology].

An evaluation of the toxic effects of three organophosphates; monocrotophos, dimethoate and methyl parathion on female reproduction was made by biochemical estimations of cytoplasmic and membrance bound proteins, lipids, phospholipids and cholesterol in the rat ovaries after treatment with their low residual level doses (LD50 1/8-1/5) to three groups of six rats each for 90 days. All the three pesticides caused degenerative changes in the ovaries as evidenced by a significant decrease in the concentration of cytoplasmic as well as membrane bound proteins, total lipids, phospholipids and cholesterol. The observations are thus indicative of the reproductive toxicity caused by organophosphates at cellular and molecular level in the ovaries of rats.

Placental morphology of rats prenatally exposed to methyl parathion.
Levario-Carrillo M., Olave M. E., Corral D. C., Alderete J. G., Gagioti S. M. and Bevilacqua E.
Exp Toxicol Pathol. 2004, Jul; 55(6):489-96.

Although prenatal exposure to pesticides has been associated with numerous adverse reproductive effects, data on the effects of such toxics in the placenta is limited. Thus, the present study was carried out to determine the morphology of the rat placenta exposed to the organophosphate pesticide methyl parathion (MP) in ad libitum fed and restricted diet animals. The pregnant females were randomly divided into control groups and experimental groups, the latter of which received MP at the doses of 0.0, 1.0, 1.5 and 2.0 mg/kg. Most cells in the maternal-fetal interface showed significant alterations in the presence of MP. Trophoblast giant cells exhibited either prominent characteristics of degeneration or normal morphology with many phagosome vacuoles, apparently containing cell debris. Vascular congestion was also more frequent in the labyrinth of the treated animals. Areas of fibrosis and hemorrhage were found in the decidua, as well as decidual cells presenting pyknotic nuclei and acidophilic cytoplasm. In the placentas of females treated with both restricted diet and MP, such changes were much more severe. Together, these alterations suggest a direct, toxic effect of MP on the placental cells. The phagocytic activity exhibited by trophoblast cells, may be playing a role in the removal of death cells from the maternal-placental interface and/or in a compensatory mechanism to maintain the uptake of maternal nutrients, following decreased metabolic exchange functions of the labyrinth due to the toxic effect of the MP.

Effect of methyl parathion formulation on estrous cycle and reproductive performance in albino rats.
Sortur S. M. and Kaliwal B. B.
Indian J Exp Biol. 1999;37(2):176-8.

The animals were injected intraperitoneally with graded doses of methyl parathion at 1.5 to 3 mg/kg body weight for 15 days from the day of estrus. Results indicated that the methyl parathion treatment showed irregular estrous cycles, affect the duration of each estrous cycle, proestrus and diestrus were significantly changed in 2.5 and 3 mg treatment groups. But there was no significant change in the number and duration of each estrous cycle, duration of proestrus and diestrus in 1.5 and 2 mg methyl parathion treatment groups. However, there was a significant decrease in the duration of estrus, while there was no significant change in the duration of metestrus in all methyl parathion treatment rats when compared with those of the corresponding parameters of the control. There was no significant effect on number of live pups on day 1 and 5 except in 3 mg methyl parathion treatment group where it was significantly decreased. There was no significant change in reproductive indices like pregnancy, parturition, live birth and viability in all the methyl parathion treatment rats except the viability index in the highest dose.

Inhibition of ovarian compensatory hypertrophy by the administration of methyl parathion in hemicastrated albino rats.
Dhondup P. and Kaliwal B. B. .
Reprod Toxicol. 1997 Jan-Feb; 11(1):77-84.

Methyl parathion, an organophosphorus pesticide that is a potent acetylcholinesterase inhibitor in animals, was administered IP in graded doses from 2.5 to 5.0 mg/kg body weight to normal hemicastrated virgin rats for 15 consecutive days. Sham-operated and hemicastrated control groups were treated with a similar quantity of olive oil vehicle. The vaginal smears and body weights of treated and control groups were recorded daily and rats were sacrificed on the 16th day. The ovaries, adrenals, liver, kidney, and uterus were removed and weighed, and the ovary from each animal was serially sectioned and stained for histologic studies. The hemicastrated control group revealed a significant increase in ovarian weight with 45% hypertrophy and a significant increase of total healthy and atretic follicles when compared with sham-operated control rats. Treatment with 2.5 and 3.5 mg methyl parathion revealed no change in the ovarian weight with 48 and 42% hypertrophy, respectively, and no change in healthy and atretic follicles when compared with hemicastrated oil-treated controls. However, treatment with 4.0 and 5.0 mg methyl parathion resulted in a significant decrease in ovarian weight gain with 13 and 8% hypertrophy, respectively, a significant decrease in the number of healthy follicles, and no change in the atretic follicles. The number of estrous cycles and duration of each estrous cycle were affected significantly with 3.5, 4.0, and 5.0 mg methyl parathion treatment when compared with controls. There were no significant changes in adrenal, liver, kidney, or uterine weight in the methyl parathion-treated groups except a decrease in uterine weight with 5.0 mg treatment when compared with oil-treated hemicastrated controls.

Temporal effect of methyl parathion on ovarian compensatory hypertrophy, follicular dynamics and estrous cycle in hemicastrated albino rats.
Asmathbanu I. and Kaliwal B. B.
J Basic Clin Physiol Pharmacol. 1997; 8(4):237-54.

Methyl parathion, an organophosphorus pesticide, was administered i.p. at a dose of 5 mg/kg body weight to hemicastrated virgin rats for 1, 5, 10 and 15 days. Treatment with methyl parathion for 1 and 5 days revealed no change in the ovarian weight with -0.64% and -9.63% hypertrophy respectively and no change in healthy and atretic follicles when compared with hemicastrated oil-treated controls. However, treatment with methyl parathion for 10 and 15 days resulted in a significant decrease in ovarian weight gain with -21.36% and -31.98% hypertrophy, respectively, a significant decrease in the number of healthy follicles, and no change in the number of atretic follicles. The number of estrous cycles and duration of each phase of the estrous cycle were significantly affected with methyl parathion treatment for 5, 10 and 15 days. However, there were no significant changes in the number of estrous cycles and duration of estrus and metestrus phases in 1 day methyl parathion treatment except for a decrease and

increase in proestrus and diestrus phases respectively. The weight of the uterus was significantly decreased whereas those of the liver, kidney and adrenal did not change in any of the methyl parathion treated groups.

Methyl parathion induced teratological study in rats.
Sunil Kumar K. B. and Devi K. S.
J Environ Biol. 1996;17(1):51-7.

Pregnant rats received daily P.O. doses of organophosphate methyl parathion (MP) from day 6 through day 15 of gestation at doses 0.5, 1 and 1.5 mg/kg body weight. Dams were sacrificed on day 20 of gestation and fetuses were examined for external and visceral anomalies. Significant decrease in dam weight gain during pregnancy and increase in resorption rate were observed in 1.5 mg MP administered rats. No increase were seen in skeletal or visceral anomalies in treatment groups, however an increase in incidence of haemorrhagic spots in brain and upper body were seen in pups from dams treated with MP.

Effect of subchronic administration of methyl parathion on in vivo protein synthesis in pregnant rats and their conceptuses.
Gupta R. C., Thornburg J. E., Stedman D. B. and Welsch F.
Toxicol Appl Pharmacol. 1984, Mar 15; 72(3):457-68.

Pregnant rats received daily po doses of the organophosphate methyl parathion (MPTH) from Day 6 through Day 15 or 19 of gestation at doses causing no (1.0 mg/kg) or minimal (1.5 mg/kg) signs of maternal toxicity. Following the dose of MPTH on Day 15 or 19, in vivo protein synthesis was measured 0.5, 1.0, and 2.0 hr after sc injection of L-[1-14C]valine at a dose of 5 microCi/mmol/100 g body wt. The specific activity of [14C]valine in the free amino acid pool and protein bound pool was significantly reduced in various regions of maternal brain and in maternal viscera, placenta, and whole embryos (Day 15), and in fetal brain and viscera (Day 19). The inhibitory effect of MPTH on net protein synthesis was dose dependent, greater on Day 19 than 15 of gestation and more pronounced in fetal than in maternal tissues.

b. <u>Studies with DPR Tox Summaries that have female reproductive endpoints</u>

Two-Generation Reproductive Study of Methyl Parathion in Rats
Bio/dynamics,Report No. BD-80-139, 7/18/82
(as summarized by California Department by Pesticide Regulation)

Methyl parathion, 93.6% pure, was given in the diet to Sprague- Dawley CD rats (15 males & 30 females/group) at 0 (acetone = vehicle), 0.5, 5.0 and 25 ppm for two generations (one litter/generation). Maternal NOEL = 5 ppm (marginal decrease in weight gain at the end of lactation); Maternal NOAEL > 25 ppm; Reproductive NOEL and NOAEL = 5 ppm (decreased pup survivability). Formerly reviewed as unacceptable

(Schreider, 3/18/85) for no justification of dose levels, no characterization of test article, no litter standardization, and incomplete histopathology. The study was upgraded to ACCEPTABLE based on an EPA Memorandum resulting in a re-review of the study. Another reevaluation of the study, prompted by the rebuttal in Record No. 086795, resulted in the decreased pup survivability being identified as a POSSIBLE ADVERSE HEALTH EFFECT. EPA One liner: Core Grade Minimum.

Three-Generation Reproductive Study of Methyl Parathion in Rats
Bayer, Report No. 053 037190,12/8/82
(as summarized by California Department by Pesticide Regulation)

Methyl parathion (95%) was given in the diet at 0, *2,* 10 and 50 ppm for a three generation study; 10 males/group, 20 females/group. There were no pups surviving at the end of F2 generation in the high dose group; NOEL = 2 ppm; UNACCEPTABLE (needs QA statement and final report revisions, no analysis of diet for test article, food consumption not measured, no clinical observations. presented, incomplete necropsy data, gestation and lactation weights included in weekly female weights), NOT UPGRADEABLE.

Three-Generation Reproductive Study of Methyl Parathion in Rats
P.M. Dolinger Assoc., Report No. 033 927643, 1979
(as summarized by California Department by Pesticide Regulation)

Summary of 3-generation study using methyl parathion (10 and 30 ppm in the diet) conducted by Woodard Research Corp. Reductions in survival noted for Fla, F1b, and F2a generations at 30 ppm and in the F-3a generation at 10 ppm; stillbirth rates were increased in F1b and F3b generations at 30 ppm; UNACCEPTABLE (no data), NOT UPGRADEABLE.
EPA One liner: Core Grade Supplementary.

SUMMARY: A consistent finding in the three rat reproduction studies on file was a decrease in pup survivability. In two of the studies (#Is 927643 and 037190) where the doses included 0, *2,* 10, 30 and 50 ppm, decreased survivability was observed at 10 ppm. In the third study (#011171) where the doses were 0, 0.5, 5.0, and 25 ppm, survivability was decreased at 25 ppm. Taken together, these data indicate decreased pup survivability is a consistent possible adverse effect with a NOEL = 5 ppm.

Teratology Study of Methyl Parathion in Rats
Research and Consulting Company AG, RCC 083553, 12/31/87
(as summarized by California Department by Pesticide Regulation)

Technical methyl parathion, batch 230 606 003, 97% pure in 0.5% aqueous Cremophor EL was administered by oral intubation to groups of 25 mated Wistar/HAN female rats at 0 (vehicle control), 0.3, 1.0 and 3.0 mg/kg/day on days 6 through 15 of gestation. An additional 10 females each were added to the 0 and 3.0 mg/kg/day groups for

cholinesterase activity measurement. **Possible adverse effects:** Decreased maternal cholinesterase activity, maternal signs of organophosphate toxicity, decreased maternal weight gain, decreased maternal food consumption, fetal developmental delay determined by decreased fetal weight and delayed ossification, and a tendency toward increased resorptions, all at 3.0 mg/kg/day. Maternal NOEL = 1.0 mg/kg/day (signs of organophosphate toxicity, cholinesterase inhibition, decreased food consumption and weight gain). Developmental NOEL = 1.0 mg/kg/day (developmental delay and marginal increase in resorptions). ACCEPTABLE study.

Teratology Study of Methyl Parathion in Rats
Bayer, 055 037196, 6/3/77
(as summarized by California Department by Pesticide Regulation)

Methyl parathion (94.4%) by oral gavage at 0, 0.1, 0.3 and 1.0 on days 6-15 of gestation; 20 pregnant females/group; fetal body weight decreased in high dose group; NOEL cannot be determined; UNACCEPTABLE (need analysis of dosing solution; need individual data for body weight, food consumption, necropsy parameters, fetal exams, fetal weights and clinical observations.), POSSIBLY UPGRADEABLE.. EPA One liner: Core Grade Supplementary.

Teratology Study of Methyl Parathion in Rats
Dolinger Assoc, 033 038392
(as summarized by California Department by Pesticide Regulation)

Summary of journal article by Fish (1966) in which rats were injected i.p. with methyl parathion on day 9 or 15 of gestation; insufficient data for evaluation. Study by Tanimura et al. (1967) suggests that one i.p. injection of methyl parathion at 15 mg/kg on day 12 of gestation reduced fetal weight. EPA One liner: Core Grade Supplementary.

Teratology Study of Methyl Parathion in Rabbits
Argus Research Laboratories, 095 111287, 11/16/91
(as summarized by California Department by Pesticide Regulation)

Methyl parathion technical (95.7% pure) was administered by gavage to artificially inseminated New Zealand White [Hra:(NZW)SPF] female rabbits (19 or 20/group) on gestation days 6 through 18 at 0 (corn oil), 0.3, 3.0, and 9.0 mg/kg/day. Maternal cholinesterase NOEL < 0.3 mg/kg/day (Significant RBC Cholinesterase inhibition occurred at > 3.0 mg/kg/day. A significant decrease in plasma Cholinesterase occurred at 9.0 mg/kg/day. Maternal Systemic NOEL: There were no significant maternal effects at any dose. Developmental NOEL = 3.0 mg/kg/day (There was an increased incidence in thickened areas of ossification in the ribs at 9.0 mg/kg/day). **Acceptable, with no adverse effects**.

Teratology Study of Methyl Parathion in Rabbits
Bayer AG, 055 037197, 9/4/84
(as summarized by California Department by Pesticide Regulation)

Methyl parathion, 95.7% pure in 0.5% aqueous Cremophor EL emulsion vehicle was administered by oral gavage to groups of 12-15 pregnant Himalayan CHBB:HM rabbits at 0 (vehicle control), 0.3, 1.0 and 3.0 mg/kg/day on days 6-18 of gestation. No adverse effects were noted. Maternal and Developmental NOEL > 3 mg/kg/day. Initially reviewed as unacceptable but possibly upgradeable with submission of justification of dosing levels, all the individual animal data, a description of the dosing solution preparation, and an analysis of the dosing solution (Parker, 12/4/85). After review of the supplemental information provided in record nos. 085035 and 088518, the study remains UNACCEPTABLE and is now considered not upgradeable due to the lack of a MTD. EPA One liner: Core Grade Minimum

Teratology Study of Methyl Parathion in Rabbits (supplement)
Bayer, 068 085035, 12/22/87
(as summarized by California Department by Pesticide Regulation)

Supplemental to record no. 037197, consisting of a retrospective range finding study in rabbits at doses of 0, 0.3, 1.0, and 3.0 mg/kg/day. The only notable finding was a minimal reduction in RBC cholinesterase activity on days 14 and 19 in the high dose group.

Teratology Study of Methyl Parathion in Rabbits (supplement)
Bayer AG, 083 088518, 12/22/87
(as summarized by California Department by Pesticide Regulation)

Supplemental to record no. 037197, consisting of a dose justification based on a rat teratology study, individual animal data, test compound analysis, and an abbreviated study protocol (G. Chernoff, 7/2/90). NOTE: Justification for the dose selection used in the rabbit teratology study (DPR Record No. 037197) has been provided in two separate documents. In the first (DPR Record No. 085035), the results of a retrospective range-finding study were presented. The only finding indicative of an MTD was a marginal decrease in RBC cholinesterase levels at 3.0 mg/kg/day, the highest dose tested. Plasma and brain cholinesterase levels were unaffected by the treatment, as were appearance, behavior, weight gain, autopsy findings, and maternal deaths. The second justification (DPR Record No. 088518), was based on the results of an unacceptable rat teratology study (DPR Record No. 037196), in which a maternal MTD was not clearly established. These data for the rat study are considered inadequate, and inappropriate for dose justification in the rabbit study. Since the demonstration of a clear MTD was not achieved in either the original rabbit teratology study, or in the retrospective range finding study, this information is not sufficient to fill the data gap. DPR Record No. 111287 (Argus Research Laboratories, 11/16/91), however, is an acceptable rabbit teratology study and therefore, the data gap is filled.

Teratology Study of Methyl Parathion in Mice
Dolinger Assoc, 033 038392, *(as summarized by California Department by Pesticide Regulation)*

Summary of journal article by Tanimura et al. (1967) in which mice were injected once i.p. with 20 or 60 mg/kg on day 10 of gestation; in high dose group 13 of 112 fetuses had cleft palate, fetal deaths elevated at the high dose level. EPA One liner: Core Grade Supplementary.

iii. Male reproductive toxicity

a. <u>studies identified in the open literature search</u>

Methyl-parathion decreases sperm function and fertilization capacity after targeting spermatocytes and maturing spermatozoa.
Piña-Guzmán B; Sánchez-Gutiérrez M; Marchetti F; Hernández-Ochoa I; Solís-Heredia MJ; Quintanilla-Vega B.
Toxicol Appl Pharmacol. 2009, Jul 15; 238(2):141-9.

Paternal germline exposure to organophosphorous pesticides (OP) has been associated with reproductive failures and adverse effects in the offspring. Methyl-parathion (Me-Pa), a worldwide-used OP, has reproductive adverse effects and is genotoxic to sperm, possibly via oxidative damage. This study investigated the stages of spermatogenesis susceptible to be targeted by Me-Pa exposure that impact on spermatozoa function and their ability to fertilize. Male mice were exposed to Me-Pa (20 mg/kg bw, i.p.) and spermatozoa from epididymis-vas deferens were collected at 7 or 28 days post-treatment (dpt) to assess the effects on maturing spermatozoa and spermatocytes, respectively. Spermatozoa were examined for DNA damage by nick translation (NT-positive cells) and SCSA (%DFI), lipoperoxidation (LPO) by malondialdehyde production, sperm function by spontaneous- and induced-acrosome reactions (AR), mitochondrial membrane potential (MMP) by using the JC-1 fluorochrome, and fertilization ability by an in vitro assay and in vivo mating. Alterations on DNA integrity (%DFI and NT-positive cells) in spermatozoa collected at 7 and 28 dpt, and decreases in sperm quality and induced-AR were observed; reduced MMP and LPO were observed at 7 dpt only. Negative correlations between LPO and sperm alterations were found. Altered sperm functional parameters evaluated either in vitro or in vivo were associated with reduced fertilization rates at both times. These results show that Me-Pa exposure of maturing spermatozoa and spermatocytes affects many sperm functional parameters that result in a decreased fertilizing capacity. Oxidative stress seems to be a likely mechanism of the detrimental effects of Me-Pa exposure in male germ cells.

Methyl parathion induces the formation of symplasts by round spermatid fusion and alters the biochemical parameters in the testis.
Narayana K.
Morphologie. 2007;91(294):173-9.

Methyl parathion (MP: O,O-dimethyl-O-4-nitrophenyl phosphorothioate) is an organophosphate pesticide used in agriculture to protect a variety of crops. Food stuffs such as fruits and vegetables could be contaminated with MP, which may be a potential route of exposure. Previous studies have shown that MP is a reproductive toxicant in animal models. The present study was designed to investigate the mechanism of symplast formation and biochemical changes that occur in the testis, following MP exposure. MP was treated to adult male Wistar rats (N=5/dose/sample time) as follows. Experiment 1 - 0, 0.75 or 1.5mg/kg/d i.p. for 25 days and experiment 2 - 0 or 3.5mg/kg/d p.o. for 25 days and sacrificed on Day 17, after the last exposure. Light microscopic examination of testis was made to evaluate the structural changes and also to establish a process of symplast formation and destruction. Quantitative biochemical estimations were made in the testis for acid phosphatase (ACP), cholesterol, total protein, uric acid, and lactate dehydrogenase (LDH). MP induced structural changes in the testis in consensus with the previous studies. The symplasts were found in the testes in experiment 1. Those cells were formed due to the cell fusion of round spermatids. The symplasts were degenerated by nuclear fragmentation. The nuclear fragments were extruded from the symplasts leaving behind only the eosinophilic cytoplasm. The cell fusion and multinucleated giant cell formation was the reason for MP induced tubular atrophy. Number of tubules with symplasts increased in experiment 1 in a dose-dependent pattern. Johnsen's scores also decreased in a dose-dependent manner in experiment 1 indicating a dose-dependent tubular destruction. The ACP, cholesterol, total protein, and LDH levels decreased in both experiments against their respective controls, whereas the uric acid level decreased in experiment 1 and increased in experiment 2 ($P < 0.01$-0.001). The effects in experiment 1 were dose-dependent. In conclusion, MP induces the formation of symplasts by cell fusion of round spermatids, which is a process involved in tubular atrophy and also induces biochemical changes in the testis.

The reproductive toxicity of the organophosphate pesticide 0, 0-dimethyl 0-4-nitrophenyl phosphorothioate (methyl parathion) in the male rat.
Prashanthi N., Narayana K., Nayanatara A., Chandra Kumar H. H., Bairy K. L. and D'Souza U. J.
Folia Morphol (Warsz). 2006;65(4):309-21.

Methyl parathion (MP) is a pesticide widely used to protect crops but also illegally used in many countries for spraying homes and businesses to contain insects. The present study was planned to investigate the effects of MP on the male reproductive organs in the rat. Male Wistar rats (13-14 weeks old) were treated with MP and sacrificed as follows. Experiment 1:0 (water vehicle), 1.75, 3.5 or 7 mg/kg (i.p.) for 5 days and sacrificed on day 14; experiment 2:0, 0.5 or 1 mg/kg (i.p.) for 12 days and sacrificed on

day 130; experiment 3: 0, 0.5 or 1 mg/kg (i.p.) for 12 days and sacrificed on day 77; experiment 4: 0, 0.75 or 1.5 mg/kg (i.p.) for 25 days and sacrificed on day 17; experiment 5: 0 or 3.5 mg/kg (p.o.) for 25 days and sacrificed on day 17 after the last exposure. The reproductive organs were removed, weighed and processed for histopathological analysis. Structural changes, for example the morphology of the epithelium and the lumina of the organs, were observed in all animals. Biochemical estimates of acid phosphatase (ACP), cholesterol, total protein, uric acid, and vitamin C were conducted in the epididymes. The weight of the epididymes increased in experiment 2 in a dose-dependent pattern ($p < 0.01$) and decreased in experiments 4 and 5 ($p < 0.01$). The weight of the ductus deferens decreased in experiment 3 at 1 mg/kg dose level ($p < 0.001$) and increased in experiment 5 ($p < 0.05$). The weight of the seminal vesicle decreased in experiment 3 at both 0.5 mg/kg and 1 mg/kg dose levels ($p < 0.001$), and increased in experiment 5 ($p < 0.01$). The weight of the prostate decreased in experiments 4 (in a dose-dependent pattern) and 5 ($p < 0.001$). ACP levels decreased in experiment 4 ($p < 0.001$) with a greater effect at 0.5 mg/kg than at 1 mg/kg. In experiment 5 ($p < 0.01$) cholesterol levels decreased to less than 50% of the control level for this experiment ($p < 0.01$) and protein levels also decreased ($p < 0.01$). Vitamin C levels decreased in a dose-dependent pattern in experiments 4 ($p < 0.001$) and 5 ($p < 0.01$). There were no effects on uric acid level. Sperm density was decreased in the epididymes of the rats treated and the epithelium of the epididymis and ductus deferens showed cellular necrosis, brush-border disruption and nuclear pyknosis. Nuclei were haloed, except in experiment 2 and the 0.5 mg/kg group of experiment 3. Methyl parathion did not induce significant changes in the structure of the seminal vesicle and prostate, except that epithelial folding was shorter than in the control. In conclusion, MP is a reproductive toxicant in the male rat and causes deterioration in the structural integrity of the reproductive organs and also the biochemical parameters in the epididymis.

Genetic damage caused by methyl-parathion in mouse spermatozoa is related to oxidative stress.
Piña-Guzmán B; Solís-Heredia MJ; Rojas-García AE; Urióstegui-Acosta M; Quintanilla-Vega B.
Toxicol Appl Pharmacol. 2006, Oct 15; 216(2):216-24.

Organophosphorous (OP) pesticides are considered genotoxic mainly to somatic cells, but results are not conclusive. Few studies have reported OP alterations on sperm chromatin and DNA, and oxidative stress has been related to their toxicity. Sperm cells are very sensitive to oxidative damage which has been associated with reproductive dysfunctions. We evaluated the effects of methyl-parathion (Me-Pa; a widely used OP) on sperm DNA, exploring the sensitive stage(s) of spermatogenesis and the relationship with oxidative stress. Male mice (10-12-weeks old) were administered Me-Pa (3-20 mg/kg bw/i.p.) and euthanized at 7- or 28-days post-treatment. Mature spermatozoa were obtained and evaluated for chromatin structure through SCSA (Sperm Chromatin Structure Assay; DNA Fragmentation Index parameters: Mean DFI and DFI%) and chromomycin-A(3) (CMA(3))-staining, for DNA damage through in situ-nick translation

(NT-positive) and for oxidative stress through lipid peroxidation (LPO; malondialdehyde production). At 7-days post-treatment (mature spermatozoa when Me-Pa exposure), dose-dependent alterations in chromatin structure (Mean DFI and CMA(3)-staining) were observed, as well as increased DNA damage, from 2-5-fold in DFI% and NT-positive cells. Chromatin alterations and DNA damage were also observed at 28-days post-treatment (cells at meiosis at the time of exposure); suggesting that the damage induced in spermatocytes was not repaired. Positive correlations were observed between LPO and sperm DNA-related parameters. These data suggest that oxidative stress is related to Me-Pa alterations on sperm DNA integrity and cells at meiosis (28-days post-treatment) and epididymal maturation (7-days post-treatment) are Me-Pa targets. These findings suggest a potential risk of Me-Pa to the offspring after transmission.

Neonatal methyl parathion exposure affects the growth and functions of the male reproductive system in the adult rat.
Narayana K., Prashanthi N., Nayanatara A., Kumar H. H., Abhilash K. and Bairy K. L. Folia Morphol (Warsz). 2006;65(1):26-33.

Methyl parathion (MP) is a well-known organophosphorus pesticide, to which humans are exposed in fruit and vegetables as residues of 0-2 mg/kg, children being at higher risk of exposure. The present study was planned to investigate the effects on the adult male reproductive functions of MP following neonatal exposure. New born male Wistar rat pups were treated orally with either 0 or 0.5 mg/kg MP from postnatal day (PND) 3 to PND 28 and sacrificed on PND 98 for the purpose of examination of the reproductive system. Methyl parathion lowered the body weights from days 10 to 24 ($p < 0.01$), the weights of the reproductive organs ($p < 0.05$-0.01), the epididymal sperm count ($p < 0.01$) and the homogenisation-resistant testicular spermatid head count ($p < 0.01$) and also decreased acid phosphatase (ACP), cholesterol, uric acid, protein, ascorbic acid, and lactate dehydrogenase ($p < 0.01$) levels in the testis but only ACP and cholesterol in the epididymis. The levels of abnormal sperm and testosterone in the testis were increased ($p < 0.01$), whereas the leutinising hormone level and total number of seminiferous tubules decreased in the testes of treated rats ($p < 0.01$). A few tubules showed exfoliation of epithelium and vacuoles. The incidence of stage XIV tubules and ratios of meiotic figures and elongating spermatids to Sertoli cell nucleoli decreased ($p < 0.01$; Mann-Whitney U test). The present results indicate that MP acts as an endocrine disruptor and consequently affects the postnatal development and growth of the male reproductive organs in the rat. These findings are important to the general public, as there is a chance of children being exposed to this pesticide.

An organophosphate insecticide methyl parathion (o- o- dimethyl o-4-nitrophenyl phosphorothioate) induces cytotoxic damage and tubular atrophy in the testis despite elevated testosterone level in the rat.
Narayana K., Prashanthi N., Nayanatara A., Bairy L. K. and D'Souza U. J.
J Toxicol Sci. 2006;31(3):177-89.

Methyl parathion (MP) is an organophosphate pesticide used in agriculture, although quite often illegally used indoors to contain insects. The present study was planned to investigate the effects of MP on rat testis. Adult male Wistar rats (13-14 weeks) were treated with MP as follows. Experiment 1-0, 1.75, 3.5 or 7 mg/kg i.p. for 5 days and sacrificed on Day 14; experiment 2 and 3- 0, 0.5, or 1 mg/kg i.p. for 12 days, and sacrificed on Days 130 and 77, respectively; experiment 4- 0, 0.75, or 1.5 mg/kg i.p. for 25 days, and sacrificed on Day 17; experiment 5- 0 or 3.5 mg/kg po for 25 days, and sacrificed on Day 17, after the last exposure. MP decreased the body weight and the testis weight in experiments 4 and 5 ($p < 0.05$-0.001) due to decreased food intake and tubular atrophy respectively. MP increased the intra-testicular testosterone level and decreased the LH level in experiments 4 and 5. The seminiferous epithelium showed sloughing of germ cells, vacuoles, focal necrosis, and formation of multinucleated giant cells, cellular degeneration (nuclear pyknosis, halo appearance and shrinkage of nuclei) and tubular atrophy, especially in experiment 4. The degree of testicular damage was higher in experiment 4>5>1>3>2 indicating more effect of prolonged i.p. treatment. Homogenization-resistant spermatid count was decreased in experiments 1, 4 and 5, and MP also decreased the tubular diameter, and epithelial height ($p < 0.05$-0.001). Incidences of stage XIV tubules, number of meiotic figures and elongating spermatids were also decreased, whereas the incidence of tubules showing epithelial sloughing increased ($p < 0.05$-0.001). We conclude that MP is a reproductive toxicant in male rats which causes significant testicular damage in the testis.

Effects of methyl parathion (o,o-dimethyl o-4-nitrophenyl phosphorothioate) on rat sperm morphology and sperm count, but not fertility, are associated with decreased ascorbic acid level in the testis.
Narayana K., Prashanthi N., Nayanatara A., Kumar H. H., Abhilash K. and Bairy K. L.
Mutat Res. 2005;588(1):28-34.

Methyl parathion (MP; o,o-dimethyl o-4-nitrophenyl phosphorothioate) is an organophosphorous pesticide used world wide to spray agricultural crops. The present study was aimed to investigate the genotoxic and cytotoxic effects on male germ cells and their possible relation with testicular ascorbic acid levels. Adult male Wistar rats (n=5/group) received MP at 0, 0.5, or 1 mg/kg (experiments 1 and 2) for 12 days and 0, 0.75 or 1.5 mg/kg (experiment 3) for 25 days (i.p.) everyday at intervals of 24 h. The epididymal sperm count, sperm abnormalities and testicular ascorbic acid levels (by 2,4-dinitrophenyl hydrazine method) were estimated on days 130, 77 and 17 following the last exposure in experiments 1, 2, and 3, respectively. Virgin untreated female rats were mated with treated males from experiments 2 and 3 for a week effective from day 35 to 41 after the first treatment, and fertility indices were measured after the birth of pups.

Sperm count was decreased in experiments 2 and 3 ($P < 0.01$), and in all three experiments, the abnormal sperms increased ($P < 0.001$). Concomitantly, the ascorbic acid levels decreased in the testis ($P < 0.05$-0.001; one-way ANOVA and Bonferroni's post hoc test). The body weights of offspring of treated males did not show significant changes from those of the controls, although there were some decreases observed. MP reduced the lactation index in experiment 2 ($P < 0.001$; Chi-square test). The number of pups/parent along with fertility indices showed some numerical decrease but without any statistical significance. The present findings suggest that MP is a weak genotoxic and cytotoxic agent in the rat exposed to human exposure dose-levels, and that these effects, except the fertility are well correlated with decreased ascorbic acid level in the testis. Furthermore, MP-induced changes in the germ cells do not have any significant effects on F1 generation.

Methyl parathion-induced sperm shape abnormalities in mouse.
Mathew G., Vijayalaxmi K. K. and Abdul Rahiman M.
Mutat Res. 1992;280(3):169-73.

Metacid 50, the commercial grade of methyl parathion (O,O-dimethyl-O-4-nitrophenyl phosphorothionate), a commonly used organophosphorus insecticide, was tested for its genotoxicity in Swiss albino mice using the sperm abnormality assay. Sperms of albino mice were examined at two time intervals, 1 week and 5 weeks after a single acute oral treatment with the pesticide at four dose levels, viz., 75.0, 37.5, 18.75 and 9.375 mg/kg body weight corresponding to 1/2 LD50, 1/4 LD50, 1/8 LD50 and 1/16 LD50 values respectively. A dose-related statistically significant increase in the percentage of abnormal sperm observed indicates the genotoxic potency of methyl parathion.

Absence of genetic and cytogenetic effects in mice treated by the organophosphorus insecticide parathion, its methyl analogue, and paraoxon.
Degraeve N. and Moutschen
J. Toxicology. 1984, Aug; 32(2):177-83.

Male mice (Q strain) received a single i.p. injection of 3 organophosphorus compounds: ethylparathion (10 mg/kg), its methyl analogue (methylparathion, 10 mg/kg), or its phosphate derivative (ethylparaoxon, 0.3 mg/kg). The number of chromosome aberrations observed in bone marrow cells and spermatogonia, and the frequency of pre- and postimplantation foetal lethality obtained in a dominant lethal mutation assay, did not conclusively prove that the tested compounds produced a mutagenic effect

B. Studies reporting no developmental or reproductive toxicity

No studies were identified in this category.

II. Epidemiologic Developmental and Reproductive Toxicity Studies

A. Studies reporting increased risk of adverse developmental or reproductive outcomes

i. Developmental toxicity

No reports were identified in this category.

ii. Female reproductive toxicity

No reports were identified in this category.

iii. Male reproductive toxicity

Sperm aneuploidy among Chinese pesticide factory workers: scoring by the FISH method.
Padungtod C., Hassold T. J., Millie E., Ryan L. M., Savitz D. A., Christiani D. C. and Xu X.
Am J Ind Med. 1999;36(2):230-8.

BACKGROUND: A study of the prevalence of sperm aneuploidy among pesticide factory workers was conducted in Anhui, China.
METHODS: We recruited 75 men: 32 subjects from a large pesticide-manufacturing plant and 43 subjects from a nearby textile factory free of pesticide exposure. Each subject met the following criteria: age of 20-40 years; continuous work in the plant for 3 months prior to the study, no congenital anomalies or acquired disease of the external genitalia and no history of recent febrile illness or mumps. Within one hour after collection from each subject, semen was evaluated in terms of several parameters and smear slides were prepared.
RESULTS: Exposure assessment revealed that workers in the pesticide plant were exposed to ethyl parathion or methamidophos, each of which is a potent organophosphate pesticide, at a median level of 0.02 mg/m3 (8-hour time weighted average as measured by personal pump) while workers in the control plant had no such occupational exposure. Twenty-nine semen slides (13 from the exposed group and 16 from the unexposed group) were randomly chosen for aneuploidy scoring by the three-color fluorescence in situ hybridization (FISH) method with scorers being unaware of

exposure status. Median semen parameters were as follows for exposed (and unexposed) men: abstinence period, 3 days (4 days); sperm concentration, 52.8x10(6)/ml (53.1x10(6)/ml); proportion of sperm with normal motility, 50.5% (61.3%); and proportion of sperm with normal morphology, 59% (61.5%). The specific chromosome abnormalities of interest were disomy for chromosome 18 and the three different types of sex chromosome disomy (i.e. XX, XY, YY disomy). The crude proportion of all aneuploidy combined was 0.30% and 0.19% for sperm from exposed and unexposed men, respectively. Poisson regression with overdispersion adjustment yielded significantly different crude risks of aneuploidy - 3.03 and 1.94 per 1,000 sperm from exposed and unexposed men, respectively - giving a rate ratio of 1.56 (95% CI, 1.06-2.31). The regression coefficients remained statistically significant after adjustment for inter-technician variability giving a rate ratio of 1.51 (95% CI, 1. 04-2.20). CONCLUSIONS: We conclude that occupational exposure to organophosphate pesticides moderately increases the prevalence of sperm aneuploidy.

Sperm chromatin alteration and DNA damage by methyl-parathion, chlorpyrifos and diazinon and their oxon metabolites in human spermatozoa.
Salazar-Arredondo E; de Jesús Solís-Heredia M; Rojas-García E; Hernández-Ochoa I; Quintanilla-Vega B.
Reprod Toxicol. 2008, Aug; 25(4):455-60.

Extensive use of organophosphorous pesticides (OP) by young men represents a public health problem. Toxicity of OP mainly results in neurotoxicity due to their oxygen analogues (oxons), formed during the OP oxidative activation. OP alter semen quality and sperm chromatin and DNA at different stages of spermatogenesis. Oxons are more toxic than the parent compounds; however, their toxicity to spermatogenic cells has not been reported. We evaluated sperm DNA damage by several OP compounds and their oxons in human spermatozoa from healthy volunteers incubated with 50-750 microM of methyl-parathion (MePA), methyl-paraoxon (MePO), chlorpyrifos (CPF), chlorpyrifos-oxon (CPO), diazinon (DZN) or diazoxon (DZO). All concentrations were not cytotoxic (evaluated by eosin-Y exclusion), except 750 microM MePO. Oxons were 15% to 10 times more toxic to sperm DNA (evaluated by the SCSA parameter, %DFI) than their corresponding parent compounds, at the following order: MePO>CPO=MePA>CPF>DZO>DZN, suggesting that oxon metabolites participate in OP sperm genotoxicity.

B. Studies reporting no increased risk of adverse developmental or reproductive outcomes

No reports were identified in this category.

III. Other Relevant Information

A. Meeting Abstracts

Prenatal toxicology of Wofatox 80 in rats.
Frosch I.
Teratology. 1990;42(2):26A.

Inhibition and recovery of rat fetal and maternal brain acetylcholinesterase (AChE) and plasma cholinesterase (ChE) after maternal exposure to a dermal dose of methyl parathion.
Kishk A. M., Abu Q., auml, e A. W., Abdel-Rahman A. H. and Abou-Donia M. B.
Toxicologist. 1998;42(1-S):38.

B. Related articles

[**Studies on DNA damage of the neuron cell in rat offspring induced by cypermerthrin and methylparathrion during embryo exposure**].
Wang J., Liu P., Wu X. and Wang F.
Wei Sheng Yan Jiu. 2007, May; 36(3):361-3. [Wei sheng yan jiu = Journal of hygiene research].

Developmental neurotoxic effects of environmental pollutants (heavy metals + organophosphates) in animal experiments.
Nagymajtäenyi L; Schulz H; Papp A; Däesi I. Neurotoxicology. 1997;18(3):876.

Mutagenic efficiency of organophosphorus insecticides used in combined treatments.
Degraeve N., Chollet M. C. and Moutschen. J. Environ Health Perspect. 1985, May; 60:395-8.

Effects of methyl parathion exposure on development and reproduction in the viviparous fish Girardinichthys multiradiatus.
Arellano-Aguilar O; Macías Garcia C.. Environ Toxicol. 2009, Apr; 24(2):178-86.

Overview of developmental heart defects by dioxins, PCBs, and pesticides.
Kopf P. G. and Walker M. K. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2009;27(4):276-85.

Decrease of muscarinic cholinergic receptors expression in placenta from rats exposed to methyl parathion.
González-García B; Olave ME; Ramos-Martínez E; González-Horta C; Levario-Carrillo M; Sánchez-Ramírez B. Hum Exp Toxicol. 2008, Mar; 27(3):241-6.

Testicular functions and serum titers of LH and testosterone in methyl parathion-fed roseringed parakeets.
Maitra S. K. and Mitra A. Ecotoxicol Environ Saf. 2008, Sep; 71(1):236-44.

Muscarinic Cholinergic Receptor Expression In Placenta From Rats Exposed To Methyl Parathion.
González-García B; Levario-Carrillo M; Ramos-Martínez E; Arévalo-Gallegos S; Infante-Ramírez R; Olave-Arreola ME; González-Horta C; Sánchez-Ramírez B. Placenta. 2006;27(1):A56.

Embryotoxicity of Methylparathion in Developing Chick.
Ullah A. and Mufti S. Birth Defects Res A Clin Mol Teratol. 2005;73(5):372.

Tropical ecotoxicity testing with Ceriodaphnia cornuta.
Do Hong L. C., Becker-Van Slooten K. and Tarradellas J. Environ Toxicol. 2004, Oct; 19(5):497-504.

Maternal and fetal acetylcholinesterase activities after repeated dermal exposure of pregnant rats to methyl parathion.
Baker R. C., Schneider K. E., Wellman S. E. and Kramer R. E. Toxicologist. 2003;72(S-1):128.

Effects of repeated developmental exposure to chlorpyrifos and methyl parathion on choline acetyltransferase and muscarinic receptors in rats.
Moore C. A., Baravik J., Meek E. C., Richardson J. R., Carr R. L. and Chambers J. E. Toxicologist. 2003;72(S-1):127.

Chicago area methyl parathion response.
McCann K. G., Moomey C. M., Runkle K. D., Hryhorczuk D. O., Clark J. M. and Barr D. B. Environ Health Perspect. 2002;110 Suppl 6:1075-8.

Inhibition of cholinesterase enzymes following a single dermal dose of chlorpyrifos and methyl parathion, alone and in combination, in pregnant rats.
Abu-Qare A. W., Abdel-Rahman A., Brownie C., Kishk A. M. and Abou-Donia M. B.. J Toxicol Environ Health A. 2001;63(3):173-89.

Inhibition and recovery of maternal and fetal cholinesterase enzyme activity following a single cutaneous dose of methyl parathion and diazinon, alone and in combination, in pregnant rats.
Abu-Qare A. W. and Abou-Donia M. B. J Appl Toxicol. 2001;21(4):307-16.

Effect of methyl parathion administration on cholinesterase activity in adult, juvenile and neonatal rats.
Beyrouty P., Deschamps Y., O'Shaughnessy D. and Pedersen K. M. Neurotoxicol Teratol. 2001;23(3):293.

Short-term and long-term survival studies in Rana tigrina tadpoles with reference to methyl parathion toxicity.
Kennedy I. J. and Sampath K. J Environ Biol. 2001;22(4):267-71.

Placental transfer and pharmacokinetics of a single dermal dose of [14C]methyl parathion in rats.
Abu-Qare A. W., Abdel-Rahman A. A., Kishk A. M. and Abou-Donia M. B. Toxicol Sci. 2000;53(1):5-12.

Activity of cholinesterase enzymes following a single dermal dose of chlorpyrifos alone, or in combination with methyl parathion in Sprague-Dawley rats.
Abou-Donia M. B. and Abu-Qare A. W. Toxicologist. 1999;48(1-S):149-50.

Placental transfer pharmacokinetics and biochemical effects following a single oral dose of (14-C)p-nitrophenol in Sprague-Dawley rats.
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