DELTAMETHRIN

This is a compilation of abstracts of articles identified during the preliminary toxicological evaluation of evidence on the developmental and reproductive toxicity of deltamethrin (CAS# 52918-63-5). Deltamethrin is a type II pyrethroid insecticide used in structural pest control, to eradicate external parasites on farm animals and to control numerous insect pests of field crops, vegetables, fruits, potted plants, and ornamentals.

The abstracts compiled below are from animal toxicity studies and epidemiologic studies reporting on developmental and reproductive sequelae related to exposure to deltamethrin 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 52 studies identified in the literature search on deltamethrin (some studies may have reported more than one adverse effect). The table below shows how deltamethrin passed the screen.

Endpoints	Reports of adverse effects		Reports of no adverse effects	
	Animal	Human	Animal	Human
Developmental	9	0	1	0
Female reproductive	0	0	0	0
Male reproductive	6	0	0	0
Total	15	0	1	0

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

- 10 other related studies (includes titles using non-traditional test species)
- 11 Publications or meeting presentations 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.

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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

Effect of prenatal exposure of deltamethrin on the ontogeny of xenobiotic metabolizing cytochrome P450s in the brain and liver of offsprings.
Johri A, Dhawan A, Lakhan Singh R, and Parmar D.
Toxicol Appl Pharmacol; (2006) 214(3):279-89.

Prenatal exposure to low doses (0.25 or 0.5 or 1.0 mg/kg, p.o.) of deltamethrin, a type II pyrethroid insecticide, to pregnant dams from gestation days 5 to 21 (GD5-21) produced dose-dependent alterations in the ontogeny of xenobiotic metabolizing cytochrome P450 (CYP) isoforms in brain and liver of the offsprings. RT-PCR analysis revealed dose-dependent increase in the mRNA expression of cerebral and hepatic CYP1A1, 1A2, 2B1, 2B2, and 2E1 isoenzymes in the offsprings exposed prenatally to deltamethrin. Similar increase in the activity of the marker enzymes of these CYP isoforms has indicated that placental transfer of the pyrethroid, a mixed type of CYP inducer, even at these low doses may be sufficient to induce the CYPs in brain and liver of the offsprings. Our data have further revealed persistence in the increase in expression of xenobiotics metabolizing CYPs up to adulthood in brain and liver of the exposed offsprings, suggesting the potential of deltamethrin to imprint the expression of CYPs in brain and liver of the offsprings following its in utero exposure. Furthermore, though the levels of CYPs were several fold lower in brain, almost equal magnitude of induction in cerebral and hepatic CYPs has further suggested that brain CYPs are responsive to the induction by environmental chemicals. The present data indicating alterations in the expression of xenobiotic metabolizing CYPs during development following prenatal exposure to deltamethrin may be of significance as these CYP enzymes are not only involved in the neurobehavioral toxicity of deltamethrin but have a role in regulating the levels of ligands that modulate growth, differentiation, and neuroendocrine functions.

Long lasting effects of prenatal exposure to deltamethrin on cerebral and hepatic cytochrome P450s and behavioral activity in rat offspring.
Johri A, Yadav S, Singh RL, Dhawan A, Ali M, and Parmar D
Eur J Pharmacol., (2006) 544(1-3):58-68.

Prenatal exposure to different doses (0.25, or 0.5 or 1.0 mg/kg corresponding to 1/320 th or 1/160 th or 1/80 th of LD50) of deltamethrin to the pregnant Wistar rats from gestation day 5 to 21 were found to produce a dose dependent increase in the activity of cytochrome P450 (CYP) dependent 7-ethoxyresorufin-O-deethylase (EROD), 7-pentoxyresorufin-O-dealkylase (PROD) and N-nitrosodimethylamine demethylase (NDMA-D) in brain and liver of offspring postnatally at 3 weeks. The increase in the activity of cytochrome P450

monooxygenases was found to be associated with the increase in the mRNA and protein expression of xenobiotic metabolizing CYP1A, 2B and 2E1 isoenzymes in the brain and liver of offspring. Dose-dependent alterations in the parameters of spontaneous locomotor activity in the offspring postnatally at 3 weeks have indicated that increase in cytochrome P450 activity may lead to the accumulation of deltamethrin and its metabolites to the levels that may be sufficient to alter the behavioral activity of the offspring. Interestingly, the inductive effect on cerebral and hepatic cytochrome P450s was found to persist postnatally up to 6 weeks in the offspring at the relatively higher doses (0.5 and 1.0 mg/kg) of deltamethrin and up to 9 weeks at the highest dose (1.0 mg/kg), though the magnitude of induction was less than that observed at 3 weeks. Alterations in the parameters of spontaneous locomotor activity in the offspring postnatally at 6 and 9 weeks, though significant only in the offspring at 3 and 6 weeks of age, have further indicated that due to the reduced activity of the cytochrome P450s during the ontogeny, the pyrethroid or its metabolites accumulating in the brain may not be cleared from the brain, thereby leading to the persistence in the increase in the expression of cerebral and hepatic cytochrome P450s in the offspring postnatally up to 9 weeks. The data suggests that low dose prenatal exposure to pyrethroids has the potential to produce long lasting effects on the expression of xenobiotic metabolizing cytochrome P450s in brain and liver of the offspring.

Perinatal exposure to deltamethrin alters dopaminergic neurochemistry in the developing mouse brain.
Richardson JR, Caudle WM, Dean ED, Wang MZ and Miller GW
Neurotoxicology (2004) 25(4):714-5

During the last decade, there has been increasing concern that children are not adequately protected from the adverse effects of pesticides. Because of this concern, many pesticides have had their uses restricted or banned. In their place, pyrethroids have become one of the pesticides of choice because they are environmentally labile and generally exhibit low mammalian toxicity. Recently, it has been shown that deltamethrin (DM), a widely used type II pyrethroid, may exert specific effects on the nigrostriatal dopaminergic system by altering striatal dopamine uptake and dopamine transporter (DAT) levels in adult mice. In this study, we sought to determine whether perinatal exposure to low levels of DM would alter dopaminergic neurochemistry in the developing mouse brain. Female C57BL/6J mice received 0 or 3 mg/kg DM in peanut butter every 3 days for 2 weeks prior to breeding. Treatment continued on the same schedule throughout gestation and lactation until the offspring were weaned on postnatal day (PND) 21. On PND 28, mice were sacrificed and the striatum was removed and frozen on dry ice for determination of monoamine levels by HPLC and dopaminergic markers by western blotting. Perinatal exposure to DM elicited no overt toxicity to either the dams or the offspring. Striatal levels of dopamine or its metabolites, DOPAC and HVA, were not affected by treatment. However, levels of the dopamine transporter (DAT) were increased by 1.9 fold, similar to that seen in adult animals exposed to higher dosages of OM. In addition, we determined the levels of the vesicular monoamine transporter 2 (VMAT2) and tyrosine hydroxylase (TH), two additional markers of dopaminergic neurons. Striatal VMAT2 levels were increased by 1.7 fold and TH levels were increased by 1.5 fold in the offspring of DM treated animals. Taken in

concert, these data suggest that the developing dopaminergic system is particularly sensitive to alterations induced by low level exposure to DM during the perinatal period.

Reproductive effects of deltamethrin on male offspring of rats exposed during pregnancy and lactation.
Andrade AJ, Araújo S, Santana GM, Ohi M, and Dalsenter PR
Regul Toxicol Pharmacol., (2002) 36(3):310-7.

The effects of low doses of deltamethrin administered to female rats on the reproductive system of male offspring were examined. The dams (n=10-12/group) were treated daily by oral gavage with 0, 1.0, 2.0, and 4.0 mg deltamethrin/kg from day 1 of pregnancy to day 21 of lactation. Maternal and reproductive outcome data and male sexual development landmarks were assessed. Fertility, sexual behavior, and a large number of reproductive endpoints, such as organ weights, sperm evaluations, testosterone concentration, and testicular histology were examined on adult male offsprings. No signs of maternal toxicity were detected at the dose levels tested. Significantly adverse effects were only seen on testicular and epididymal absolute weights and the diameter of seminiferous tubules in the group treated with the highest dose of deltamethrin (4.0 mg/kg). The results indicate that in utero and lactational exposure to deltamethrin may induce subtle changes in reproductive behavior and physiology of male offspring rats at dose levels that do not cause maternal toxicity.

Effects of prenatal exposure to deltamethrin on forced swimming behavior, motor activity, and striatal dopamine levels in male and female rats.
Lazarini CA, Florio JC, Lemonica IP, Bernardi MM
Neurotoxicol Teratol., (2001) 23(6):665-73.

The effects of prenatal exposure of rat pups to 0.08 mg/kg deltamethrin (DTM) on physical, reflex and behavioral developmental parameters, on forced swimming and open-field behaviors, and on striatal monoamine levels at 60 days of age were observed. Maternal and offspring body weight, physical and reflex development were unaffected by the exposure to the pesticide. At 21 days of age, open-field locomotion frequency and immobility duration of male and female offspring were not different between control and exposed animals. However, male rearing frequency was increased in experimental animals. A decreased immobility latency to float and in general activity after the swimming test in male offspring was observed at adult age; no interference was detected in the float duration during the swimming test. In addition, these animals presented higher striatal 3,4-dihydroxyphenylacetic acid (DOPAC) levels without modification in dopamine (DA) levels and an increased DOPAC/DA ratio. These data indicate a higher activity of the dopaminergic system in these animals. Noradrenaline (NA) levels were increased, while MHPG levels were not detectable in the system studied. Serotonin (5-HT) and 5-hydroxyindolacetic acid (5-HIAA) levels, as well as the homovanillic acid (HVA)/DA ratio, were not modified by the exposure to the pesticide. No changes were observed in swimming and open-field behaviors nor were there any changes in striatal monoamines or their metabolites in the female experimental group. In relation to the pesticide formula, the

present data showing that prenatal exposure to DTM alters latency to float and the activity of striatal dopaminergic system might reflect a persistent effect of the pesticide on animal motor activity, mainly in males. On the other hand, the decrease in general activity observed in experimental male rats suggests higher levels of emotionality induced by previous exposure to the swimming behavior test in relation to control animals. Data gathered in the present study may be important for the assessment of the safety of pyrethroid insecticides.

Neurodevelopmental consequences of gestational exposure (GD14-GD20) to low dose deltamethrin in rats.
Aziz MH, Agrawal AK, Adhami VM. Shukla Y, and Seth PK
Neurosci Lett., (2001) 16; 300(3):161-5.

Effect of low level in utero exposure to deltamethrin (DT) (1mg /kg wt.) during gestation day 14-20 was studied on selected neurobehavioral, neurochemical, immunohistochemical parameters in rats at 6 and 12 weeks postnatal period. The significant increase in acetylcholinesterase activity and decrease in (3)H-quinuclidinyl benzilate binding in the hippocampal region of DT exposed animals, suggesting impairment in cholinergic (muscarinic) receptors. A significant decrease in the learning and memory performances was also observed both at 6 and 12 weeks, which is directly correlated with decrease in muscarinic receptor binding. Immunohistochemistry and image analysis of growth associated protein-43, a neuron specific protein present in axonal growth cone and a marker for neuronal differentiation and synaptogenesis, exhibit aberrant increase in its expression in the hippocampus in DT exposed rats at both time periods. The data suggests that low level exposure to DT in utero during brain growth spurt period adversely affects the developing brain and the changes persist even up to 12 weeks postnatal period in rats. Although there is no significant recovery at 12 weeks assessment but still significant impairment persist on biochemical and behavioural parameters.

Studies on the teratogenic effects of deltamethrin in rats.
Abdel-Khalik MM, Hanafy MS Abdel-Aziz MI
Dtsch Tierarztl Wochenschr. (1993), Apr; 100(4):142-3.

Deltamethrin is a pyrethroid insecticide used to eradicate external parasites on farm animals. Residues of this pesticide were shown to be present in food from animal origin which encouraged us to investigate the effects of deltamethrin on foetuses of pregnant rats. Literature search shows that previous research was focused on organochlorine and organophosphate pesticides whereas little attention was given to the newer pyrethroid insecticides. Four groups of pregnant rats (20 rats each) were given either the vehicle (control) or doses of 1, 2.5 or 5 mg/kg b. w. of deltamethrin orally from day 6 to day 15 of pregnancy which was terminated by killing the animals on the 19th day for foetal examinations. The incidence of early embryonic deaths was higher in deltamethrin-treated rats than in control females. Deltamethrin caused retardation of growth, hypoplasia of the lungs, dilatation of the renal pelvis and increase in placental weight. No skeletal changes were observed in foetuses recovered from deltamethrin-treated females. Although

deltamethrin is relatively safe, however its effects on the foetus should be considered when used on pregnant animals or in environments where pregnant animals and women live.

Neurotoxic effects of deltamethrin, a synthetic pyrethroid during early development in rats.
Husain R, and Seth PK,
International Journal of Toxicology, Occupational and Environmental Health. (1991) 1(1):138

Deltamethrin (DT), a Type II synthetic pyrethroid insecticide produces central nervous system dysfunction in adult mammals, but very little is known about its effect on immature animals. The present study reports the pre- and postnatal effect of DT on reflex ontogeny, key enzymes of neurotransmission, polyamine levels and behavior in neonatal rats. Timed pregnant rats were administered DT (7.0 mg/mg b. wt.) orally, daily from day 5 to 21 of gestation. Neonates were exposed in a similar manner from day 22 to 37 postnatally. Controls of both the treatment groups received the vehicle in an identical manner. The pups exposed to DT gestationally, showed reduced birth weight and growth rate, also ontogeny of various reflexes and developmental landmarks were delayed. A significant decrease in the activity of monoamine oxidase, Na+,(K+)-ATPase and acetylcholinesterase accompanied with an overall decrease in the levels of regional brain polyamines was envisaged. The neonates on exposure to DT exhibited a significant increase in monoamine oxidase while polyamine concentration exhibited a differential effect, with an overall increase in several brain areas. Results suggest that DT adversely affects morphogenesis, growth, maturation, and function of the brain. The alterations in polyamine levels in specific brain regions by DT, further confirms the perturbations in maturation profiles of specific neuronal cell populations.

Placental histogenesis and the cardiotoxic effect in rat progeny under the influence of the synthetic pyrethroid Decis.
Badaeva LN, and Nedorenko NI
Vrach Delo., (1991) (10):68-71.

A study is presented of the placenta histogenesis and development of cardiotoxic effect in rat progeny under the effect of the synthetic pyrethroid decis. The drug was introduced to pregnant animals perorally in 1/20 and 1/100 LD50 doses during the critical periods of neonatal development. Morphological disorders were revealed as well as a reduction of enzymatic activity (OP, SDG) in the placenta and ultrastructural and histochemical disorders of these enzymes in the myocardium of the progeny at different periods of ontogenesis. The revealed changes evidence the capacity of the pyrethroid decis to penetrate through the placental barrier and produce a cardiolesioning effect on the progeny.

b. Studies with DPR Tox Summaries that have developmental endpoints

Two-Generation Reproductive Study of Deltamethrin in Rats
Argus Research Laboratories, Inc, Report No. 136; 172624; 1/17/92
(as summarized by California Department by Pesticide Regulation)

Thirty rats/sex/group were dosed in the diet with 0, 5, 20, 80 or 320 ppm of Deltamethrin technical (purity: 99.7%) for two generations. The treatment period for the P1 parents included 82 days prior to mating, the mating period, 3 weeks of gestation and 3 weeks of lactation. At that time, 30 F1 animals/sex/group were selected as parents and treated for a minimum of 86 days in the premating period, the mating period, and 3 weeks both for the gestation and lactation periods. For the P1 generation, one female in the 320 ppm group died as a result of the treatment. The only clinical signs exhibited by the P1 generation were the high dose females during the lactation period when the uptake of the active ingredient was at the highest level. These signs included ataxia and hypersensitivity. The high dose group for the F1 generation suffered 17 male and 19 female treatmentrelated mortalities between days 2 and 44 of the premating period. Clinical signs manifested by these animals included ataxia, urine stained abdominal fur, impaired righting reflex, splayed limbs and vocalization. The signs became less severe as the animals aged and consumed a lower relative quantity of the test material. The mean body weights and food consumption values of the 320 ppm treatment group of both generations were lower than those of the controls ($p<0.01$). Although the absolute and relative organ weights were significantly reduced or increased in comparison to the control values, there was no apparent treatment-related effect upon any of these organs. The gross examination revealed that 9/28 males and 12/28 females in the F1 high dose group suffered blood clots in either the subdural or epidural region of the brain. All of these animals died between day 2 and 44 of the premating period. There were no treatment-related effects upon the reproductive parameters. The mean pup weights for the high dose group in both generations were not significantly different from those of the controls at the time of birth. However, by day 7 of the lactation period, the mean weights of these pups were less than those of the controls ($p<0.01$). In addition, the F1 pups in the 320 ppm treatment group suffered increased mortality between days 4 and 21 of lactation. This effect was not evident in the F2 group. **No adverse reproductive effects** indicated. **Parental NOEL**: 80 ppm (based upon the clinical signs, increased mortality, lower body weight and reduced food consumption noted for the 320 ppm treatment group) ((M) 5.4 to 5.8 mg/kg/day, (F) 5.2 to 10.6 mg/kg/day), **Reproductive NOEL**: 320 ppm (no treatment-related effect on reproductive parameters at highest dose tested) ((M) 21.2 to 24.9 mg/kg/day, (F) 21.8 to 37.3 mg/kg/day), **Developmental NOEL**: 80 ppm (based upon lower mean pup body weights for both generations and increased mortality for the F1 pups during the lactation period in the 320 ppm treatment group); Study **acceptable**. (Moore, 2/3/00)

Teratology Study of Deltamethrin in Rabbits
International Research and Development Corporation, Report No. 004 129658; 5/7/90
(as summarized by California Department by Pesticide Regulation)

Deltamethrin technical (purity of 99.2%, lot 8N 0701 B2) was administered by oral gavage to 16 inseminated New Zealand White SPF female rabbits/dose at levels of 10, 25 and 100 mg/kg/day. Mortality- one high-dose doe died on gestation day 27 with congestion of the lungs; death at 10 mg/kg/day not considered compound-related; maternal NOEL = 25 mg/kg/day (based on mortality at high dose); Fetal morphology- no dose-related malformations; variations (high-dose) included wrist flexure and retardation of ossification in hyoid body, pubic bones and unossified tail bones. Developmental
NOEL = 25 mg/kg (based on retardation of bone ossification); NOAEL(M/F)=100 mg/kg/day; **No Adverse Effects**; **ACCEPTABLE**. Kellner, 7/18/95.

ii. Female reproductive toxicity

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

No studies for female reproductive endpoints were found in the open literature.

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

Two-Generation Reproductive Study of Deltamethrin in Rats
Argus Research Laboratories, Inc, Report No. 136; 172624; 1/17/92
(as summarized by California Department by Pesticide Regulation)

Thirty rats/sex/group were dosed in the diet with 0, 5, 20, 80 or 320 ppm of Deltamethrin technical (purity: 99.7%) for two generations. The treatment period for the P1 parents included 82 days prior to mating, the mating period, 3 weeks of gestation and 3 weeks of lactation. At that time, 30 F1 animals/sex/group were selected as parents and treated for a minimum of 86 days in the premating period, the mating period, and 3 weeks both for the gestation and lactation periods. For the P1 generation, one female in the 320 ppm group died as a result of the treatment. The only clinical signs exhibited by the P1 generation were the high dose females during the lactation period when the uptake of the active ingredient was at the highest level. These signs included ataxia and hypersensitivity. The high dose group for the F1 generation suffered 17 male and 19 female treatmentrelated mortalities between days 2 and 44 of the premating period. Clinical signs manifested by these animals included ataxia, urine stained abdominal fur, impaired righting reflex, splayed limbs and vocalization. The signs became less severe as the animals aged and consumed a lower relative quantity of the test material. The mean body weights and food consumption values of the 320 ppm treatment group of both generations were lower than those of the controls ($p<0.01$). Although the absolute and relative organ weights were significantly reduced or increased in comparison to the control values, there was no apparent treatment-related effect upon any of these organs. The gross examination revealed that 9/28 males and 12/28 females in the F1

high dose group suffered blood clots in either the subdural or epidural region of the brain. All of these animals died between day 2 and 44 of the premating period. There were no treatment-related effects upon the reproductive parameters. The mean pup weights for the high dose group in both generations were not significantly different from those of the controls at the time of birth. However, by day 7 of the lactation period, the mean weights of these pups were less than those of the controls ($p<0.01$). In addition, the F1 pups in the 320 ppm treatment group suffered increased mortality between days 4 and 21 of lactation. This effect was not evident in the F2 group. **No adverse reproductive effects** indicated. **Parental NOEL**: 80 ppm (based upon the clinical signs, increased mortality, lower body weight and reduced food consumption noted for the 320 ppm treatment group) ((M) 5.4 to 5.8 mg/kg/day, (F) 5.2 to 10.6 mg/kg/day), **Reproductive NOEL**: 320 ppm (no treatment-related effect on reproductive parameters at highest dose tested) ((M) 21.2 to 24.9 mg/kg/day, (F) 21.8 to 37.3 mg/kg/day), **Developmental NOEL**: 80 ppm (based upon lower mean pup body weights for both generations and increased mortality for the F1 pups during the lactation period in the 320 ppm treatment group); Study **acceptable**. (Moore, 2/3/00)

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iii. Male reproductive toxicity

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

Comparative effects of dimethoate and deltamethrin on reproductive system in male mice.
Abdallah FB, Slima AB, Dammak I, Keskes-Ammar L, and Mallek Z
Andrologia. (2010) 42(3):182-6.

The effects of dimethoate (5, 15 and 28 mg kg(-1) day(-1)), deltamethrin (5 mg kg(-1) day(-1)) and their mixture (5 mg kg(-1) day(-1)) on male reproduction in mice were studied. The insecticides were given orally by gavage to male mice for 21 days. At the end of the treatment period, body, testes and epididymides weights and sperm parameters were determined. Alone mixture treatment has significantly decreased body weights. Dimethoate at 28 mg kg(-1) day(-1), deltamethrin at 5 mg kg(-1) day(-1) and their mixture at 5 mg kg(-1) day(-1) were associated with a significantly decreased sperm count, motility and viability and significantly increased percent morphologically abnormal spermatozoa compared with the controls. This study demonstrated the adverse effects of dimethoate at high dose, deltamethrin and their combining at 5 mg kg(-1)day(-1) on reproductive system and sperm parameters in male mice.

Toxic responses to deltamethrin (DM) low doses on gonads, sex hormones and lipoperoxidation in male rats following subcutaneous treatments.
Issam C, Samir H, Zohra H, Monia Z, and Hassen BC
J Toxicol Sci. (2009) 34(6):663-70.

Deltamethrin (DM) is a alpha- cyano pyrethroid insecticide used extensively in pest control. Although initially thought to be least toxic, a number of recent reports showed its toxicity in mammalian and non-mammalian laboratory and wildlife animal species. The present study,

carried out in male rats, is a contribution to explore some mechanisms underlying DM toxicity. The aim of the present research was to investigate the effect of different subcutaneous treatments with DM (2 ppm for 30 days, 20 ppm for 45 days and 200 ppm for 60 days) on testes histopathology, sex hormones and oxidative stress from male rats. Our study mentioned an hypospermatogenesis within the testes accompanied by some apoptotic figures in particular cell fragments into the seminiferous tubules (ST)' lumen. The results obtained show that follicule-stimulating hormone (FSH), luteinizing hormone (LH) and testosterone can be differently influenced in rats. In fact, findings of the present investigation mention a significant decrease ($p <$ or $= 0.05$) of FSH, LH and testosterone at the highest DM dose. Whereas a significant reduction of FSH was noticed after 45 days of treatment, the assessment of oxidative stress by malondialdehyde (MDA) measurements in plasma revealed a significant increase of this parameter after 30 days, 45 days or 60 days. In conclusion the study shows that subcutaneous DM treatment produces an arrest of spermatogenesis, a significant disharmony in sex hormones and MDA levels in rats that is related to dose, length of treatment and to the lipid peroxidation which may be one of the molecular mechanisms involved in DM-induced gonads toxicity.

Reproductive effects of deltamethrin on male offspring of rats exposed during pregnancy and lactation.
Andrade AJ, Araújo S, Santana GM, Ohi M, and Dalsenter PR
Regul Toxicol Pharmacol., (2002) 36(3):310-7.

The effects of low doses of deltamethrin administered to female rats on the reproductive system of male offspring were examined. The dams (n=10-12/group) were treated daily by oral gavage with 0, 1.0, 2.0, and 4.0 mg deltamethrin/kg from day 1 of pregnancy to day 21 of lactation. Maternal and reproductive outcome data and male sexual development landmarks were assessed. Fertility, sexual behavior, and a large number of reproductive endpoints, such as organ weights, sperm evaluations, testosterone concentration, and testicular histology were examined on adult male offsprings. No signs of maternal toxicity were detected at the dose levels tested. Significantly adverse effects were only seen on testicular and epididymal absolute weights and the diameter of seminiferous tubules in the group treated with the highest dose of deltamethrin (4.0 mg/kg). The results indicate that in utero and lactational exposure to deltamethrin may induce subtle changes in reproductive behavior and physiology of male offspring rats at dose levels that do not cause maternal toxicity.

Deltamethrin-induced testicular apoptosis in rats: the protective effect of nitric oxide synthase inhibitor.
El-Gohary M, Awara WM., Nassar S, and Hawas S.
Toxicology. (1999) 132(1):1-8.

This study is the first to examine and characterize the testicular apoptosis which might be induced due to exposure of male rats to deltamethrin. Furthermore, the role which might be played by nitric oxide (NO), as well as the other reactive oxygen species (ROS) in controlling this testicular apoptosis was assessed. Apoptosis was evaluated by DNA

fragmentation detected by agarose gel electrophoresis and cellular morphology on testicular tissue sections. It was found that administration of deltamethrin (1 mg/kg daily for 21 days) to animals resulted in characteristic DNA migration patterns (laddering), thereby providing evidence that apoptosis is the major mechanism of cell death in the testicular tissues. In addition, histopathological examination of testicular tissue sections showed that apoptosis was confined to the basal germ cells, primary and secondary spermatocytes. These changes, in addition to the appearance of Sertoli cell vacuoles in deltamethrin-intoxicated animals, indicate the suppression of spermatogenesis. At the same time, the plasma levels of both NO and lipid peroxides measured as malondialdehyde (MDA) were found to be significantly increased in deltamethrin-treated animals. Administration of NO synthase (NOS) inhibitors such as N(G)-nitro monomethyl L-arginine hydrochloride (L-NMMA, 1 mg/kg) to rats 2 h before exposure to deltamethrin was effective in the reduction of the typically testicular apoptotic DNA fragmentation pattern and the associated histopathological changes. These findings may suggest that deltamethrin-induced testicular apoptosis is mediated by NO. Therefore, the pharmacological manipulation of apoptosisby selective NOS inhibitors such as L-NMMA may offer new possibilities for the control of deltamethrin-induced testicular dysfunction and infertility in the future.

Influence of diazinon and deltamethrin on reproductive organs and fertility of male rats.
Abd el-Aziz MI, Sahlab AM, and Abd el-Khalik M.
Dtsch Tierarztl Wochenschr., (1994) 101(6):230-2.

The effect of diazinon and deltamethrine at two dosage levels on male reproductive tissues was studied. The tested doses were given orally to male rats for 65 consecutive days. Sex organs weight analysis, semen picture, testosterone levels and the conception rate were the criteria used to evaluate the productive efficiency of the treated rats. Both doses of diazinon and deltamethrine decreased the weights of most genital organs and motility associated with an increase in the percentage of dead and morphologically abnormal spermatozoa of treated rats. A decrease in the plasma testosterone level was observed in all treated groups. Oral administration of diazinon and deltamethrine for 65 consecutive days decreased the conception rate in non-treated females (mated with treated male).

Effect of organophosphorus (dimethoate) and pyrethroid (deltamethrin) pesticides on semen characteristics in rabbits.
Salem MH, Abo-Elezz Z, Abd-Allah GA, Hassan GA and Shaker N
J Environ Sci Health B (1988); 23(3):279-90.

The present study was undertaken to determine the effect of chronic treatment with two sublethal doses of Dimethoate (organo-phosphorus) or Deltamethrin (pyrethroid) on body weight and semen characteristics in adult male rabbits. Pesticide treatment resulted in a decline in body weight, libido, ejaculate volume, sperm concentration and semen initial fructose; and an increase in abnormal and dead sperm and methylene blue reduction time. In this regard Dimethoate showed greater effects than Deltamethrin. The hazardous effect of these pesticides on semen quality continued during the post-treatment period, and was

dose-dependent. This deleterious effect on sperm formation together with the decline in libido suggests a decrease in testosterone secretion by pesticide treatment.

B. Studies reporting no developmental or reproductive toxicity

a. Studies identified in the open literature search

Toxicity studies with decamethrin, a synthetic pyrethroid insecticide.
Kavlock R, Chernoff N, Baron R, Linder R, Rogers E, Carver B, Dilley J, and Simmon V
J Environ Pathol Toxicol., (1979) 2(3):751-65.

Decamethrin is a synthetic pyrethroid insecticide that has been under investigation by the World Health Organization for use in some vector control programs. Decamethrin proved to be a highly toxic pyrethroid ester. The acute LD50 for adult female rats was 31 mg/kg by the oral route and 4 mg/kg by the intravenous route of administration. The LD50 was observed to be sex and age dependent, with higher values recorded for weanlings and males. Initial signs of decamethrin poisoning include profuse salivation and convulsive movements. Weakness, dyspnea, anorexia and staining of the fur were observed beyond the first day following compound administration. Absorption of decamethrin was rapid by the inhalation route and minimal by the dermal route of administration. No evidence of teratogenic activity was found in rats or mice at dose levels that produced marked maternal toxicity, and no persistent toxicity was observed in neonatal rats that received perinatal exposure to decamethrin. No mutagenic activity was detected in three different in vitro assays, with or without metabolic activation.

b. Studies with DPR Tox Summaries that have developmental or reproductive endpoints

Three-Generation Reproductive Study of Deltamethrin in Rats
International Research and Development Corporation, Report No. 014 129682; 2/5/80
(as summarized by California Department by Pesticide Regulation)

Deltamethrin technical (lot 22, purity not stated) was administered in the diet to 10 male and 20 female Charles River CD* rats/dose/generation beginning about 76 days before mating and continuing through sacrifice at levels of 0, 2, 20 and 50 ppm for three generations; decreased mean parental body weight of the F0 males in the 50 ppm dosage group; slight reductions in mean food consumption in 50 ppm F1 males and F2 females; Parental NOEL = 20 ppm; reduced mean pup body weights at lactation day 21 in F1, F2 and F3 litters. **No Adverse Effects** (no reproductive toxicity at any dosage level tested); Reproductive NOEL=50 ppm; **UNACCEPTABLE** but **possibly upgradeable** with submission of test article purity, adequate dose level justification and full histopathology of parental animals. Kellner, 7/21/95.

II. Epidemiologic Developmental and Reproductive Toxicity Studies

There were no reports identified for this category.

III. Other Relevant Information

A. Meeting Abstracts

Reproducibility of developmental neurotoxicity produced by pyrethroids and DDT in neonatal mice.
Ray DE, Verschoyle RD, and Muhammad BY. Toxicologist (2002) Mar 66(1-S):131

B. Related articles

An in vitro study on reproductive toxicology of Deltamethrin on rat spermatozoa.
Abdallah FB, Hamden K, Galeraud-Denis I, El Feki A and Keskes-Ammar L. Andrologia (2010). 42(4):254-9.

Developmental neurotoxicity of pyrethroid insecticides in zebrafish embryos.
DeMicco A, Cooper KR, Richardson JR, and White LA. Toxicol Sci., (2010) 113(1):177-86.

Simultaneous exposure to low concentrations of dichlorodiphenyltrichloroethane, deltamethrin, nonylphenol and phytoestrogens has negative effects on the reproductive parameters in male Spraque-Dawley rats.
Kilian E, Delport R, Bornman MS and de Jager C. Andrologia. (2007) 39(4):128-35.

Effects of deltamethrin on neurobehavioral development of offspring of intoxicated rats.
Li T, Li GH, Chen L, Wu YT, Chen JH and Shi N Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. [Zhonghua lao dong wei sheng zhi ye bing za zhi = Zhonghua laodong weisheng zhiyebing zazhi = Chinese journal of industrial hygiene and occupational diseases] (2006) 24(6):330-2.

Reproductive evaluation of two pesticides combined (deltamethrin and endosulfan) in female rats.
Presibella KM, Kita DH, Carneiro CB, Andrade AJ, and Dalsenter PR. Reprod Toxicol., (2005) 20(1):95-101.

Effects of currently used pesticides in assays for estrogenicity, androgenicity, and aromatase activity *in vitro*.
Andersen HR, Vinggaard AM, Rasmussen TH, Gjermandsen IM and Bonefeld-Jorgensen EC.Toxicol Appl Pharmacol., (2002) 179(1):1-12.

Mutagenic evaluation of deltamethrin using rodent dominant lethal assay.
Shukla Y, and Taneja P. Mutat Res; (2000) 467(2):119-27.

Measurements of toxicity and critical stages of development.
Hoffman DJ. Wildlife Toxicology and Population Modeling: Integrated Studies of Agroecosystems (SETAC Special Publications series): (1994) 47-67

Additional endpoints and overview of a mouse skeletal variant assay for detecting exposure to teratogens.
Beck SL. Teratology. (1993) 47(2):147-57

Toxicity of lindane, atrazine, and deltamethrin to early life stages of zebrafish (Brachydanio rerio).
George G, and Nagel R. Ecotoxicol Environ Saf., (1990) 20(3):246-55.

The effect of acute maternal toxicity on fetal development in the mouse.
Kavlock RJ, Chernoff N and Rogers EH. Teratog Carcinog Mutagen., (1985) 5(1):3-13.

C. Publications with a relevant title but no abstract

Comment on: Effect of prenatal exposure of deltamethrin on the ontogeny of xenobiotic metabolizing cytochrome P450s in the brain and liver of offsprings [Johri et al. Toxicol Appl Pharmacol. 2006 Aug 1;214(3):279-89 (medline/16494911)].
Crofton KM, Harrill JA, and Wolansky MJ. Toxicol Appl Pharmacol., (2007) 1; 218(1):96-7;

Differential responses of regional brain polyamines following in utero exposure to synthetic pyrethroid insecticides: a preliminary report.
Husain R, Malaviya M, Seth PK, and Husain R. Bull Environ Contam Toxicol., (1992) 49(3):402-9.

Further evaluation of an in vivo teratology screen.
Kavlock RJ, Short RD Jr, and Chernoff N. Teratog Carcinog Mutagen., (1987) 7:7-16.

An evaluation of figure-eight maze activity and general behavioral development following prenatal exposure to forty chemicals: effects of cytosine arabinoside, dinocap, nitrofen, and vitamin A.
Gray LE Jr, Kavlock RJ, Ostby J, Ferrell J, Rogers J, Gray K. Neurotoxicology (Little Rock, AR) (1986) 7:449-462.

Validation of an in vivo developmental toxicity screen in the mouse.
Seidenberg JM, Anderson DG, Becker RA. Teratog Carcinog Mutagen., (1986) 6:361-374.

The effect of acute maternal toxicity on fetal development in the mouse.
Kavlock RJ., Chernoff N and Rogers EH. Teratog Carcinog Mutagen., (1985) 5:3-13.

An extended evaluation of an in vivo teratology screen utilizing postnatal growth and viability in the mouse.
Gray LE Jr, and Kavlock RJ. Teratog Carcinog Mutagen., (1984) 4:403-426.

Assessment of the utility of postnatal testing following prenatal exposure to forty chemicals.
Gray LE Jr, Kavlock RJ, Ostby J, and Ferrell J. Prog Clin Biol Res., (1983)140:39-62

An in vivo teratology screen utilizing pregnant mice.
Chernoff N and Kavlock RJ. J Toxicol Environ Health., (1982) 10:541-550

A reseach protocol for postnatal evaluation of teratogenic effects.
Gray LE Jr, Kavlock RJ, Chernoff N. Teratology (1980) 21:41A

Effects of acute maternal toxicity upon fetal development in the mouse.
Kavlock RJ, and Chernoff N. Teratology (1980) 21:48A

Toxicity studies with decamethrin, a synthetic pyrethroid insecticide.
Kavlock R, Chernoff N, Baron R, Linder R, Rogers E, Carver B, Dilley J and Simmon V. J Environ Path Toxicol., (1979) 2:751-765.