EVIDENCE ON DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF PROGESTERONE

Reproductive and Cancer Hazard Assessment Section (RCHAS)
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California Environmental Protection Agency (Cal/EPA)
Progesterone Pharmacokinetics

• Low oral bioavailability
  – Vaginal, nasal, dermal bioavailability
  – Micronized progesterone orally bioavailable
• Short half life (5 min in serum)
• Metabolized in liver
• Activates progesterone receptors
Progesterone Exposure

- Contraception (IUD)
- IVF pregnancy support
- Gynecological disorders
- Hormone replacement therapy
- Supplement/cosmetic
- Livestock growth promoter
- Environmental contaminant
Male Reproductive Effects

• Humans
  – 1958, 8-9 prison volunteers, 50 mg/d i.m., 10 weeks
    • Azoospermia
    • Reduced libido and testicular size
    • Fewer mature sperm in seminiferous tubules
  – 2003, 10 young men, 50 mg/d i.m., 7 days
    • Reduced LH, FSH, testosterone, GNRH response

• Animals
  – Spermatogenesis, monkeys, rabbits, rats
  – Altered sexual development, rats
Female Reproductive Effects

- **Humans**
  - 1956, 32 women, 300 mg oral
    - Suppressed ovulation
  - 1982, 80 women, progesterone IUD
    - Lower postpartum menstruation
    - Greater milk production, altered composition

- **Animals**
  - Reduced fertility, several species
  - Altered sexual development
  - Parturition and maternal behavior
Developmental Toxicity-Human

• Malformation
  – Six studies including progesterone-treated women
  – No statistically confirmed associations

• Pregnancy outcome
  – Three prospective random studies
  – No statistically confirmed effects

• Female virilization
  – Confirmed for several progestagens
  – Only case reports for progesterone

• Male hypospadias
  – Progestagen case-control studies
  – Two progesterone studies; no control groups
Developmental Toxicity-Animals

• Pregnancy outcome
  – Rats, intrauterine death and growth retardation
  – Rats, rabbits, altered sex ratio of newborns
  – No increase in malformations

• Altered sexual development
  – Two studies in mice
  – Impaired adult mating in males
  – Enhanced postpartum aggression in females
Developmental Toxicity-Animals

• Female virilization/anogenital distance
  – Nor-testosterone effects confirmed in animals
  – 2/10 progesterone studies found anogenital distance effects

• Male hypospadias/anogenital distance
  – Six studies
  – Increases, decreases, no effects on anogenital distance
Summary of DART Effects Reported for Progesterone

Developmental
  • Intrauterine death and reduced fetal weight
  • Altered male and female sexual development

Male Reproductive
  • Suppressed spermatogenesis
  • Reduced fertility, altered sexual development

Female Reproductive
  • Suppressed ovulation
  • Reduced fertility, altered sexual development