

Proposition 65 Listing Mechanisms (Informational Agenda Item)

Office of Environmental Health Hazard Assessment

Developmental and Reproductive Toxicant
Identification Committee Meeting

Sacramento, California
July 12–13, 2011

Overview

- ▶ Listing mechanisms
- ▶ Number of listings by mechanism
- ▶ Authority for each mechanism
- ▶ Procedure for implementing each mechanism
- ▶ An example of a recent listing for each method
- ▶ Questions

Identifying Chemicals as Known to the State to Cause Reproductive Toxicity under Proposition 65

- ▶ Chemicals known to cause reproductive toxicity can be:
 1. identified by the State's Qualified Experts
 2. identified via California Labor Code provisions
 3. formally required to be labeled or identified by California state or Federal government
 4. formally identified by an Authoritative Body

Proposition 65 DART Listings (Total = 302)

Endpoint	Number of Listings
Developmental only	208
Female Reproductive only	1
Male Reproductive only	22
Developmental and Female	14
Developmental and Male	24
Female and Male	9
Developmental, Female and Male	24

DART Listings by Mechanism

Mechanism	Number of Listings
State's Qualified Experts	37
Labor Code	25
Formally Required	168
Authoritative Bodies	74

“State’s Qualified Experts”

“A chemical is known to the state to cause ... reproductive toxicity if in the opinion of the state’s qualified experts it has been clearly shown by scientifically valid testing according to generally accepted principles to cause reproductive toxicity.”

State's Qualified Experts Procedure

- ▶ OEHHA screens chemicals for possible DART effects using Prioritization Procedure (2004)
- ▶ At DART IC meeting, committee provides advice on priority
- ▶ Based on committee advice, OEHHA chooses chemicals for development of hazard identification materials (HIM)
- ▶ Committee reviews HIM and decides whether or not the chemical has been clearly shown to cause reproductive toxicity
 - Committee has criteria for listing adopted in 1993

Example of State's Qualified Experts Listing

- ▶ **Chromium (hexavalent compounds)**
 - Recommended by DART IC for HIM preparation on 12/10/07
 - 60 day data call-in for HIM began 1/18/08
 - HIM sent to DART IC and released for public comment 9/5/08
 - Considered by DART IC for listing 11/20/08
 - Vote: developmental – 7 for, 0 against, 1 recusal
female repro – 6 for, 1 against, 1 recusal
male repro – 7 for, 0 against, 1 recusal
 - Listed for developmental, female and male endpoints 12/19/08

Labor Code

- ▶ The Proposition 65 list “shall include at a minimum those substances identified by reference in Labor Code Section 6382(b)(1) and ... additionally by reference in Labor Code Section 6382(d)”
 - Includes chemicals in Federal Hazard Communications Standards (i.e., identified as causing reproductive toxicity by OSHA or ACGIH)

Labor Code Procedure

- ▶ OEHHA monitors publications identifying chemicals that are covered by Labor Code §6382(b)(1) or (d)
- ▶ Notice of Intent to List published in the *California Regulatory Notice Register* (30 day public comment period)
- ▶ Comments submitted reviewed by OEHHA
- ▶ Chemicals meeting statutory requirements are listed
- ▶ Chemicals not meeting requirements are reviewed for other listing mechanisms

Examples of Labor Code Listings

Chemical	CAS No.	Endpoint	Reference
N,N-dimethylacetamide	127-19-5	Developmental	ACGIH (2009)*
Ethylene oxide	75-21-8	Male reproduction Female reproduction Developmental	29 CFR part 1910, Sub-part Z

*Justification: The ACGIH Threshold Limit Value was based in part on embryo/fetal damage.

“Formally Required”

- ▶ “A chemical is known to the state to cause ... reproductive toxicity if ... an agency of the state or federal government has formally required it to be labeled or identified as causing ... reproductive toxicity.”

“Formally Required” Procedure

- ▶ Chemicals required to be labeled or identified by a state or federal agency as causing reproductive toxicity
- ▶ Notice of Intent to List published in the CRNR (30 day public comment period)
- ▶ Comments submitted reviewed by OEHHA
- ▶ Chemicals meeting statutory requirements are listed
- ▶ Chemicals not meeting requirements are reviewed for other listing mechanisms

Example of “Formally Required” Listing

Chemical	Toxicological Endpoint	References
Nimodipine CAS No. 66085-59-4	Developmental toxicity	FDA (1996)*

*Food and Drug Administration (FDA) approved the required package insert for the drug nimodipine in 1996. The package insert described potential developmental effects associated with use of the drug.

FDA Required Package Insert for Nimodipine

Nimodipine (Under PRECAUTIONS: Pregnancy)

“Pregnancy Category C.

Nimodipine has been shown to have a teratogenic effect in Himalayan rabbits. ...Nimodipine was embryotoxic, causing resorption and stunted growth of fetuses, in Long Evans rats. ...In two other rat studies, ...higher incidences of skeletal variation, stunted fetuses and stillbirths [were seen].”

“Authoritative Bodies”

- ▶ “A chemical is known to the state to cause reproductive toxicity if ... a body considered to be authoritative by [the state’s qualified experts] has formally identified it as causing ... reproductive toxicity.”

Authoritative Bodies for Reproductive Toxicity

Authoritative Body	Effective
International Agency for Research on Cancer (IARC)	1989 – present*
National Institute for Occupational Safety and Health (NIOSH)	1990 – present
National Toxicology Program (NTP)	1989 – 1998 2002 – present**
U.S. Environmental Protection Agency (U.S. EPA)	1989 – present
U.S. Food and Drug Administration (U.S. FDA)	1990 – present

* solely as to transplacental carcinogenicity since 1998

** solely as to final reports of NTP's Center for the Evaluation of Risks to Human Reproduction (CERHR)

DART-IC Input into Authoritative Bodies Listing Process

- ▶ DART-IC designates Authoritative Bodies
 - Last updated by DART-IC in 2002
- ▶ DART-IC is provided notices of possible listings and given the opportunity to comment prior to the listing of a given chemical

Authoritative Bodies Procedure

- ▶ OEHHA monitors lists, reports or documents appearing to meet regulatory criteria
- ▶ OEHHA publishes a request for relevant information in CRNR (60 day public comment period)
 - If OEHHA determines regulatory criteria are not met, the chemical is tracked and evaluated for other listing mechanisms
- ▶ OEHHA publishes a Notice of Intent to List in the CRNR (30 day public comment period)
- ▶ If criteria specified in regulations are met, the chemical is listed (Notice of Listing published in the CRNR)
- ▶ If criteria are not met, chemical is referred to the SQE

Authoritative Bodies (AB) Regulatory Listing Criteria

1. Formal identification criteria
2. Scientific criteria

AB Formal Identification Criteria

Identification criteria

The chemical is ...

- 1 on an AB-issued list as causing reproductive toxicity, **or**
- 2 the subject of a published AB report concluding the it causes reproductive toxicity, **or**
- 3 otherwise identified as causing reproductive toxicity by the AB in a document that indicates the identification is a final action

Formality criteria

- 1 Chemical is accurately identified, **and**
- 2 **One** of the following has occurred:
 - ▶ review by advisory committee in public meeting,
 - ▶ public review and comment,
 - ▶ published in a publication (e.g., Federal Register),
 - ▶ signed by institution head or designee,
 - ▶ adoption as a final rule by AB
 - ▶ set forth in official document used for regulatory purposes

AB Scientific Criteria for “As Causing Reproductive Toxicity”

- ▶ Human studies – indicate a causal relationship between the chemical and reproductive toxicity, or
- ▶ Animal studies – There are sufficient data indicating
 - a biologically plausible association between adverse human reproductive effects and the toxic agent, taking into account the adequacy of the experimental design and other parameters , e.g.,
 - route of administration,
 - frequency and duration of exposure,
 - numbers of test animals,
 - choice of species,
 - choice of dosage levels, and
 - consideration of maternal toxicity

Recent Authoritative Body Listings (since 2002)

Authoritative Body	Chemicals Listed for DART
IARC	--
NIOSH	Di (2-ethylhexyl) phthalate ¹ 1,3-Butadiene ² Acrylamide ³
NTP-CERHR	1-Bromopropane 2-Bromopropane Butyl benzyl phthalate Di- <i>n</i> -butyl phthalate Di- <i>n</i> -hexyl phthalate Di-isodecyl phthalate Acrylamide ³
U.S. EPA	Triphenyltin hydroxide 1,3-Butadiene ² Molinate Nitrobenzene
U.S. FDA	Di (2-ethylhexyl) phthalate ¹

¹ Documents from NIOSH and U.S. FDA used in listing

² Documents from NIOSH and U.S. EPA used in listing

³ Documents from NIOSH and NTP-CERHR used in listing

Example of AB Listing: Acrylamide

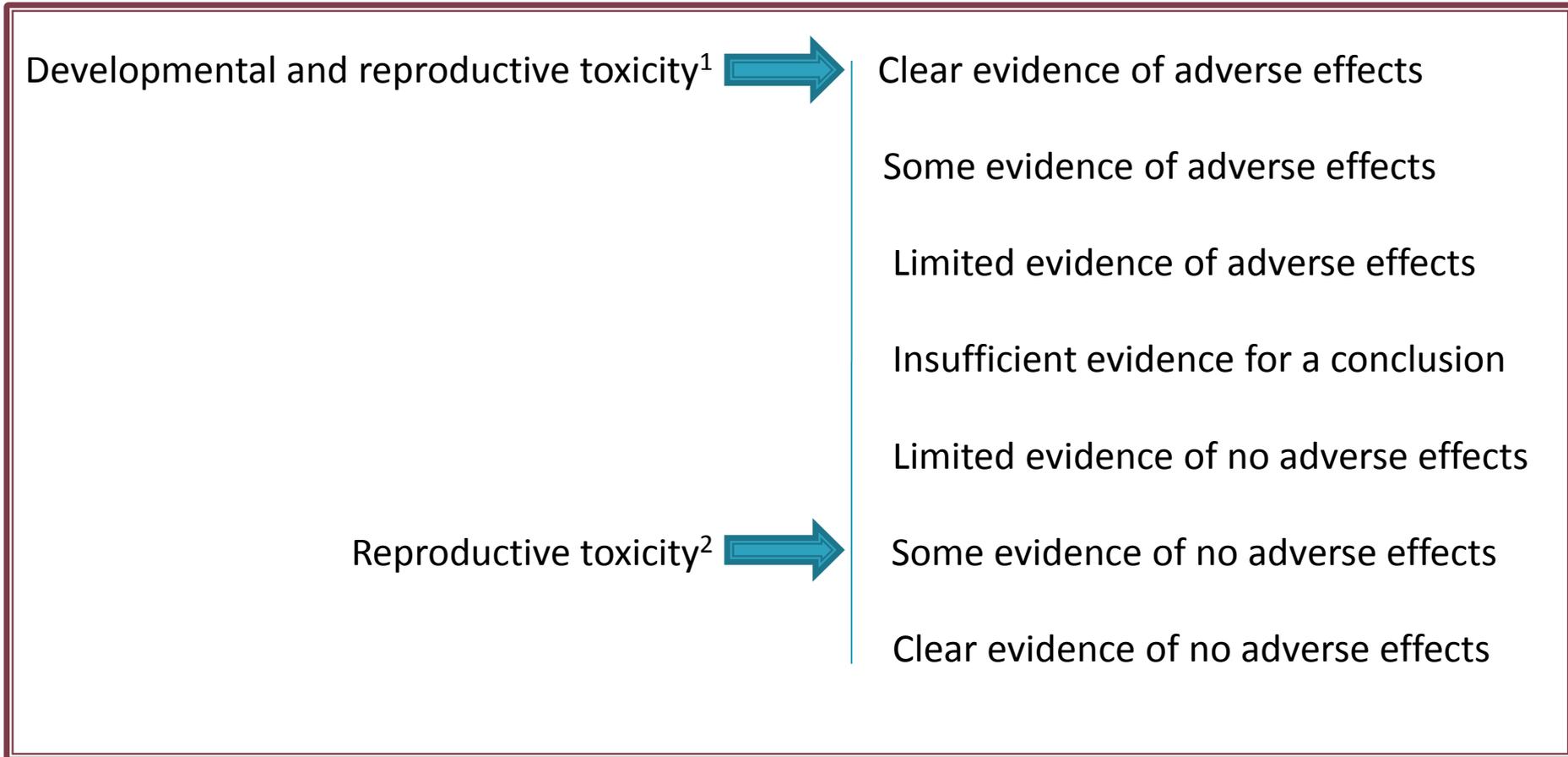
Chemical	Listing Date	Toxicological Endpoints	Reference
Acrylamide CAS No. 79-06-1		developmental toxicity male reproductive toxicity	NIOSH (1991) NIOSH (1992) NTP CERHR (2005)

References:

- NIOSH, 1991. NIOH and NIOSH basis for an occupational health standard – Acrylamide: A review of the literature. US Department of Health and Human Services in cooperation with the National Institute of Occupational Health, Solna, Sweden.
- NIOSH, 1992. Occupational Safety and Health Guideline for Acrylamide.
- NTP-CERHR, 2005. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Acrylamide.

NTP-CERHR Monograph on Acrylamide

Figure 2. The weight of evidence that acrylamide causes adverse developmental or reproductive effects in animals



¹ reproductive effects in male mice and rats

² for female mice and rats

AB Listing of Acrylamide Formal Identification by NTP-CERHR

NTP-CERHR (2005) Monograph on the Potential Human Reproductive and Developmental Effects of Acrylamide:

“Data are sufficient to conclude that acrylamide is a *developmental toxicant in rats...*

The rat and mouse data are assumed relevant to the assessment of potential effects in humans.”

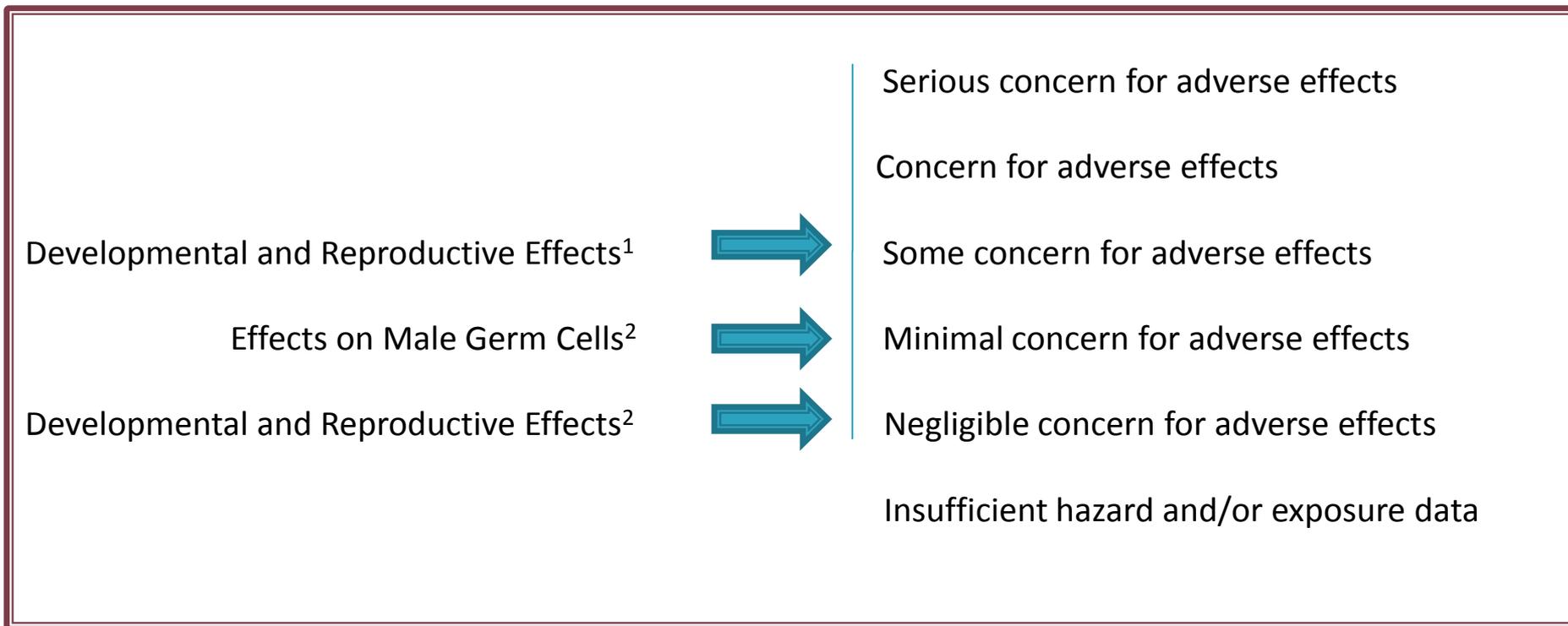
“The data are sufficient to conclude that acrylamide is a *reproductive toxicant in male rats...*

Data are sufficient to conclude that acrylamide is a *reproductive toxicant in male mice.*

The rat and mouse data are assumed relevant to assessment of human reproductive risk.”

NTP-CERHR Monograph on Acrylamide

Figure 3. NTP conclusions regarding the possibilities that human development or reproduction could be adversely affected by exposure to acrylamide



¹ for occupational exposures (includes mutagenic effects on male germ cells)

² for the general population

AB Listing of Acrylamide

Studies and Relevant Endpoints Relied On by NTP-CERHR

Developmental

- ▶ Decreased fetal weight per litter (Field et al., 1990)
- ▶ Increased resorptions and decreased litter size (Sakamoto and Hashimoto, 1986)
- ▶ Increased post-implantation loss in cohabited females (Zenick et al., 1986)
- ▶ Increased pre- and post-implantation loss (Sublet et al., 1989)
- ▶ Decreased live litter size in two generations (Chapin et al., 1995)
- ▶ Decreased live litter size and increased post-implantation loss in two generations (Tyl et al., 2000b)

Male Reproductive

- ▶ Decreased litter size, decreased pregnancy rate and increased resorptions (Sakamoto and Hashimoto, 1986)
- ▶ Impaired ejaculation, decreased vaginal and uterine sperm and pregnancy rates and increased post-implantation loss in cohabited females (Zenick et al., 1986)
- ▶ Increased pre- and post-implantation loss, decreased uterine sperm in cohabited females, decreased uterine sperm motility, decrease fertilization of oocytes (Sublet et al., 1989)
- ▶ Decreased live litter size in two generations (Chapin et al., 1995)
- ▶ Decreased live litter size and increased post-implantation loss in two generations (Tyl et al., 2000b)

AB Listing of Acrylamide Formal Identification by NIOSH

NIOSH (1991) concluded that:

“...acrylamide monomer may be ...hazardous to reproduction. Recent studies confirm that acrylamide exposures cause ...reproductive effects in animals....”

“Acrylamide exposure affected both fetal and postnatal development in mouse and rat offspring when dams were orally dosed during pregnancy. Neurotoxic effects occurred in neonates when the dam drank water containing acrylamide concentrations that were not toxic to her.”

NIOSH (1992) stated that:

“Acrylamide is ...a reproductive toxin...”

Male reproductive effects reported in NIOSH (1991, 1992):

testicular degeneration, decreased testosterone levels, decreased fertility, and dominant lethal effects in exposed experimental animals.

Developmental effects reported:

nerve degeneration, decreased birth weight and decreased weight gain in the offspring of animals exposed to acrylamide during pregnancy.

AB Listing of Acrylamide

Studies and Relevant Endpoints Relied on by NIOSH

- Developmental
 - Decreased birth weight (Zenick et al., 1986)
 - Changes in various intestinal enzyme concentrations measured in the neonate (Walden et al., 1981)
 - Wallerian degeneration of tibial nerve, unilateral optic nerve degeneration (American Cyanamid Company, 1980)
 - Increased resorptions per litter, decreased litter size (Nalco Chemical Co., 1987)
- Male reproductive
 - Decrease number of litters (fecundity index), increased preimplantation loss (Nalco Chemical Co., 1987)
 - Testicular degeneration (Hashimoto et al., 1981, NML, 1991)
 - Decreased fertility rate, decreased number fetuses/dam, increased number resorptions/dam (Sakamoto and Hashimoto, 1986)
 - Decreased copulatory performance (Zenick et al., 1986)
 - Increased pre- or post- implantation loss (Sublet et al., 1986, Shelby et al, 1986)
 - Dose-dependent decrease of testosterone (Ali et al., 1983)
 - Chromosomal alterations in sperm cells (Sakamoto and Hashimoto, 1986)

Listing of Avermectin B1 via U.S. EPA as an AB

Chemical	CAS No.	Endpoint	Pesticide status or usage	Reference
avermectin B1 (abamectin)	71751-41-2	developmental toxicity	Registered in CA	U.S. EPA (1994a,b; 2005)

U.S. EPA (1994a). Proposed Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know. *Federal Register 59: 1788*.

U.S. EPA (1994b). Final Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know. *Federal Register 59(229): 61432*.

U.S. EPA (2005). Avermectin B1 and its delta-8,9-isomer; Pesticide Tolerance. Final Rule. *Federal Register 70(31):7876-7886*.

AB Listing of Avermectin B1 Formal Identification by U.S. EPA

U.S. EPA (1994a and 1994b):

“...there is sufficient evidence for listing abamectin [avermectin B1] on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available developmental toxicity data.”

Increased susceptibility (qualitative and/or quantitative) was seen in prenatal developmental toxicity studies in CD-1 mice and rabbits following in utero exposure to avermectin B1. There was also an increase in quantitative and qualitative susceptibility in the rat reproductive toxicity study.

U.S. EPA (2005):

- identified three studies in mice, rabbits and rats as demonstrating developmental toxicity, and
- used the NOEL for developmental toxicity in the rat reproductive toxicity study as the basis for the reference doses (RfDs) for chronic dietary, short-term and intermediate-term incidental oral, dermal, and inhalation exposures in humans.

AB Listing of Avermectin B1 Studies and Relevant Endpoints Relied on by U.S. EPA

U.S EPA (2005)

- ▶ Prenatal developmental study in rodents – CD-1 mouse
 - Developmental NOAEL < 0.75 mg/ kg/day
 - Developmental LOAEL = 0.75 mg/ kg/day based on cleft palate and hindlimb extension
- ▶ Prenatal developmental study in nonrodents – rabbits
 - Developmental NOAEL = 1.0 mg/kg/day
 - Developmental LOAEL = 2.0 mg/kg/ day based on cleft palate, clubbed foot, delayed ossification of sternebrae, metacarpals, phalanges
- ▶ 2-Generation reproduction and fertility effects study – rat
 - Offspring NOAEL = 0.12 mg/kg/day
 - Offspring LOAEL = 0.40 mg/kg/ day based on increased retinal folds, increased dead pups at birth, decreased viability and lactation indices, decreased pup body weight

Questions?