

# Maximum Allowable Dose Level Development Under Proposition 65

Office of Environmental Health Hazard Assessment  
California Environmental Protection Agency

Developmental and Reproductive Toxicant (DART)  
Identification Committee Meeting

March 18, 2013

# Basis for Developing Maximum Allowable Dose Levels (“MADLs”)

Proposition 65 Statute requires:

- “clear and reasonable warning” for “knowingly and intentionally” exposing individuals to listed chemicals
- Prohibition of discharge of listed chemicals to sources of drinking water

Except when:

- “...the exposure will have no observable effect assuming exposure at one thousand (1,000) times the level in question.”

(Health and Safety Code, Section 25249.10(c))

# MADLs as “Safe Harbors”

- ▣ Deemed in regulation as having no effect when multiplied by 1000, consistent with statute
- ▣ Aid to businesses in complying with Proposition 65
- ▣ Aid the public in determining significant exposures
- ▣ Adopted in regulation following processes established in law and regulations

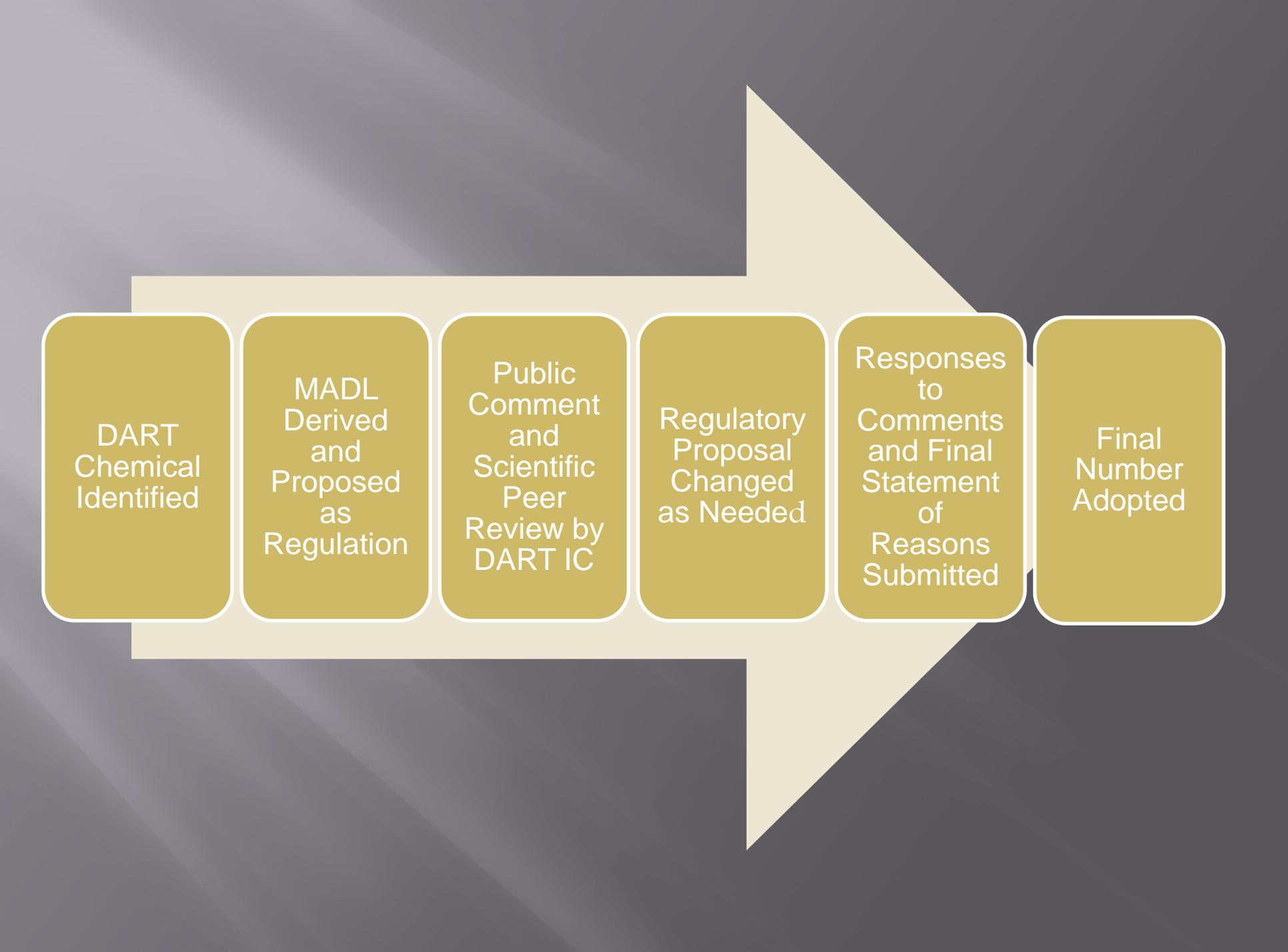
# Alternative Analyses

- ▣ “Nothing shall preclude a person from using evidence, standards, assessment methodologies, principles, assumptions or levels not described in this article to establish that a level of exposure has no observable effect at one thousand (1,000) times the level in question.”

(Title 27 Cal. Code of Regs., Section 25801(a))

# DART IC Members Peer Review MADLs

- ▣ Scientific basis for regulations adopted by any California Environmental Protection Agency (Cal/EPA) entity must be peer reviewed (Health and Safety Code section 57004)
  - OEHHA develops MADLs and is within Cal/EPA
  - MADLs subject to scientific peer review
- ▣ The DART IC members are identified peer reviewers of the scientific basis of MADLs (Title 27 Cal. Code of Regs., section 25305(b)(6))



DART  
Chemical  
Identified

MADL  
Derived  
and  
Proposed  
as  
Regulation

Public  
Comment  
and  
Scientific  
Peer  
Review by  
DART IC

Regulatory  
Proposal  
Changed  
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Responses  
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Final  
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**Sent to DART IC:**

- **ISOR/Scientific Basis**
- **Public Notice**
- **If requested, references**

# MADL Peer Review Process

- ▣ Regulatory package for proposed MADL sent to DART IC members
  - Members requested to only review scientific basis
  - Other regulatory package elements sent as FYI
- ▣ Members can be compensated for their time peer reviewing MADLs
- ▣ Individual members submit comments to OEHHA (address identified in request letter)
- ▣ Consensus among members is not required
- ▣ Comments considered in MADL development. Responses to DART IC comments part of administrative record

# What is a MADL?

Maximum Allowable Dose Level is defined in regulation (Title 27 Cal. Code of Regs., section 25801(b)(1))

- A level of exposure shall be deemed to have no observable effect, assuming exposure at one thousand times that level, provided that the level is determined by means of an assessment defined in the regulation
- The maximum dose level having no observable effect (“NOEL”) is divided by one thousand (1,000) to arrive at the maximum allowable dose level

# What Data Are Used In MADL Development?

- The determination of whether a level of exposure to a chemical known to the state to cause reproductive toxicity has no observable effect shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of the chemical.
- Only studies producing the reproductive effect which provides the basis for listing shall be utilized for the determination of the NOEL.
- Where multiple reproductive effects provide the basis for listing, the reproductive effect for which studies produce the lowest NOEL shall be utilized for the determination of the NOEL.

(Title 27 Cal. Code of Regs., sections 25801 and 25803)

# How Are MADLs Developed?

- The NOEL shall be the highest dose level which results in no observable reproductive effect expressed in milligrams of chemical per kilogram of bodyweight per day.
- The NOEL shall be based on the most sensitive study deemed to be of sufficient quality.
- The NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL.
  - Male (adult) effect - 70 kilograms
  - Female or conceptus effect - 58 kilograms
  - Child reproductive effect – other body weights
- When available data are of such quality that anatomic, physiologic, pharmacokinetic and metabolic considerations can be taken into account with confidence, they may be used in the assessment.
- When data do not allow the determination of a NOEL, the lowest observable effect level (LOEL) shall be divided by 10 to establish a NOEL for purposes of assessment.

# Example of MADL Calculation (1)

- “Methyl bromide as a structural fumigant”
  - Developmental toxicity
  - Inhalation exposure
  - NOEL of 40 ppm in rabbits
- Conversion of air concentration in ppm to mg/m<sup>3</sup> using a conversion factor of 3.89
  - $40 \text{ ppm} \times 3.89 = 155.60 \text{ mg/m}^3$
- Conversion of air concentration (mg/m<sup>3</sup>) from 6 hours per day to the equivalent concentration for 24 hours per day
  - $155.60 \text{ mg/m}^3 \times 6 \text{ hr} / 24 \text{ hr} = 38.90 \text{ mg/m}^3$
- Calculation of the NOEL expressed as mg/kg-day
  - Reported body weight of 4.19 kg of pregnant rabbits in the group exposed to 40 ppm methyl bromide on GD 20, using the inhalation rate of 1.512 m<sup>3</sup>/day
  - $(38.90 \text{ mg/m}^3 \times 1.512 \text{ m}^3/\text{day}) / (4.19 \text{ kg}) = 14.04 \text{ mg/kg-day}$
- Calculation of the NOEL in mg/day for a 58 kg pregnant woman
  - $14.04 \text{ mg/kg-day} \times 58 \text{ kg} = 814.30 \text{ mg/day}$
- MADL derived by dividing the NOEL by one thousand
- **MADL<sub>inhalation</sub>** =  $814.30 \text{ mg/day} / 1000 = 814.30 \text{ } \mu\text{g/day}$ , or **810  $\mu\text{g/day}$**  after rounding.

# Deviation From Default

“In the absence of principles or assumptions scientifically more appropriate based upon the available data, defaults apply.”

(Title 27 Cal. Code of Regs., Section 25803(a))

# Example of MADL Calculation (2)

- Di(2-ethylhexyl)phthalate (DEHP)
  - Developmental, male reproductive toxicity
  - Oral exposure
  - NOEL of 5.8 mg/kg-day found in rats
- Calculation of the NOEL for a 70 kg man
  - $5.8 \text{ mg/kg-day} \times 70 \text{ kg} = 406.0 \text{ mg/day}$
- MADL derived by dividing the NOEL by one thousand
- **MADL<sub>adult oral</sub> = 406 mg/day / 1000 = 406 µg/day or 410 µg/day after rounding.**
  
- For infants 0-2 years of age, the average body weight of 10 kg over this developmental period used (Section 25703(a)(8); National Center for Health Statistics, 2005)
  - Calculation of the NOEL for a 10 kg infant
  - $5.8 \text{ mg/kg-day} \times 10 \text{ kg} = 58 \text{ mg/day}$
  - **MADL<sub>infant oral</sub> = 58 mg/day / 1000 = 58 µg/day.**
  
- For neonates, the 50<sup>th</sup> percentile birth weight for boys of 3.5 kg used (National Center for Health Statistics, 2005)
  - Calculation of the NOEL for a 3.5 kg neonate
  - $5.8 \text{ mg/kg-day} \times 3.5 \text{ kg} = 20.3 \text{ mg/day} = 20 \text{ mg/day (rounded)}$
  - **MADL<sub>neonate oral</sub> = 20 mg/day / 1000 = 20 µg/day.**