Data Summary

- **Epidemiology:**
  - 9 studies looked at 8 reproductive / developmental measures
  - 6 of 8 measures = no associations
  - 1 measure (spontaneous abortion) shown to be a false positive by a far more robust negative study
  - 1 measure (neural tube defect) was equivocal (one + / one -)

- **Toxicology:**
  - State of the art study = no developmental toxicity
  - State of the art 2-generation study = no reproductive toxicity
  - 3 Hypothesis-generating studies under physiologically unrealistic circumstances are not relevant to humans exposed to BDCM in chlorinated water
Epidemiology and toxicology studies indicate that BDCM has not been clearly shown to be a reproductive toxicant in humans or laboratory animals.
Approach

- Review and evaluate relevant and available epidemiology and toxicology data

- Major data sources:
  - Review by Graves et al., 2001
  - Review by Tardiff et al., 2006
  - An additional epidemiology study: Nieuwenhuijsen et al., 2007
  - An additional toxicology study: Bielmeier et al., 2007
Epidemiology Findings Related to BDCM

- **Oral cleft**: 1 study, no association  
  [Dodds & King, 2001]

- **Cardiac defects**: 1 study, no association  
  [Dodds & King, 2001]

- **Chromosomal abnormalities**:  
  1 study, no association  
  [Dodds & King, 2001]

- **Stillbirth**: 1 study, no association  
  [Dodds et al., 2004]

- **Intra-uterine growth retardation**:  
  3 studies, no association  
  [Infante-Rivard, 2004; Hinkley et al., 2005; Porter et al., 2005]
Epidemiology Findings Related to BDCM (cont)

- **Small for gestational age**: 1 study, no association [Wright et al., 2004]
- **Preterm delivery**: 2 studies, no association [Wright et al., 2004; Savitz et al., 2005]
- ** Neural tube defects**: 2 studies, results equivocal [(+) Dodds & King, 2001; (-) Klotz & Pyrch, 1998]
- **Spontaneous abortion**: 2 studies, one association [Waller et al., 1998] followed by another of far more robust design with no association [Savitz et al., 2005]
Epidemiology studies indicate that BDCM has not been clearly shown to be a reproductive toxicant in humans.
Two-generation contemporary design for BDCM continuously in tap water (30 P/dose group)

- Doses to SD rats = 0, 50, 150, 450, and 900 mg/L (= 0 to 109 mg/kg-day)
- No abnormalities observed in F1 & F2
- Statistically significant effects at 2 top doses of P & F1: Mortality & clinical signs associated with reduced absolute and relative water intake, reduced body weights & gains, & reduced feed consumption, delayed sexual maturation
- No toxicity in F2 generation
- NOAEL for F1 = at least 50 mg/L
  ($\approx$ 4.1 – 12.6 mg/kg-day or 5,125 – 15,750 times human adult exposure)
One-generation contemporary design for BDCM in tap water (25/dose group)

Doses:
- SD rats = 0, 50, 150, 450, and 900 mg/L [= 0 to 82 mg/kg-day]
- SPF rabbits = 0, 15, 150, 450, and 900 mg/L [= 0 to 55 mg/kg-day]

Maternal pathology in rats & rabbits:
- Reduced abs. & rel. H2O consumption (≥ 50 ppm)
- Reduced body weight gain (≥ 450 ppm)
- Reduced relative food consumption (≥ 450 ppm)

Additional maternal pathology in rabbits:
- Weight loss (900 ppm)

No skeletal changes & no changes in embryo-fetal viability
Pathology in Rat Fetuses
◆ Minimal delay in ossification of forepaws & phalanges & hindpaws & metatarsals (900 ppm); effects were marginal, reversible, & associated with severely reduced maternal weight gain

NOAEL, Maternal:
◆ Rat = 18.4 mg/kg-day (150 ppm)
◆ Rabbit = 13.4 mg/kg-day (150 ppm)

NOAEL, Developmental:
◆ Rat = 45 mg/kg-day (450 ppm)
◆ Rabbit = 55.3 mg/kg-day (900 ppm)

Margin of Exposure: ≈ 56,000 to 70,000 between developmental NOAEL (rat, rabbit) and human doses [≈ 0.0008 mg/kg-day]
Epidemiology:
- 9 studies looked at 8 reproductive / developmental measures
- 6 of 8 measures = no associations
- 1 measure (SAB) showed to be a false positive by a far more robust negative study
- 1 measure (NTD) was equivocal (one + / one -)

Toxicology:
- State of the art study = no developmental toxicity
- State of the art 2-generation study = no reproductive toxicity
- 3 Hypothesis-generating studies at physiologically unrealistic circumstances are not relevant to humans exposed to BDCM in chlorinated water
Overall Conclusion

- Epidemiology and toxicology studies indicate that BDCM has not been clearly shown to be a reproductive toxicant in humans or laboratory animals.
Proposition 65 exempts drinking water:
See Sections 12502 and 25249.11 of Statute
Q & A

- Thank you