OEHHA's Review of DPR's Draft Methyl Iodide Risk Assessment

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OEHHA's responsibility and role

- OEHHA and DPR are both part of Cal/EPA
- OEHHA is the Cal/EPA lead for risk assessment
- OEHHA has legal mandates to provide advice, consultation, and recommendations to DPR regarding human health risk associated with pesticide exposures
- OEHHA reviews draft risk assessments developed by DPR

Primary reviewers

- Dr. Joseph Brown
- Dr. John Budroe
- Dr. Elaine Khan
- Dr. Charles Salocks
- Dr. David Ting
- Dr. Kathleen Vork

Methyl iodide (MeI) risk assessment

Topics to be covered in this presentation:

- Toxicity assessment
  - non-cancer endpoints
    - several possible MOAs
    - uncertainty in the PBPK modeling of the reproductive endpoint
  - genotoxicity and cancer endpoints
- Exposure assessment

Hazard identification of non-cancer endpoints

- Key adverse health effects:
  - fetal death in rabbit
  - neurotoxicity in rat
  - olfactory epithelial degeneration in rat
  - change in organ weight and body weight gain in rat
  - perturbation of thyroid hormone regulation in rat and rabbit
  - salivary gland metaplasia in rat

Critical NOAEL for non-cancer endpoints

- The lowest NOAEL (2 ppm) is derived from a developmental toxicity study (Nemec, 2002)
  - female rabbits (24/group)
  - inhalation exposure (0, 2, 10, and 20 ppm) between GD 6 through 28, sacrificed on GD 29
  - many developmental effects, including reduced fetal weight, reduced viable fetuses, and increased late resorption and fetal death

Acute exposure is the “risk driver” for non-cancer endpoints

- Acute exposure is important, because:
  - it has the lowest NOAEL
  - it would protect against effects from longer exposures
  - represents highest air concentration

Uncertainties in the PBPK Modeling of the reproductive endpoint

- A complex model
- Assumed excess serum iodide is the sole MOA
- Inter-species differences in the distribution of and responses to serum iodide are not fully accounted for
- Some key model parameters are based on sparse data

Acute exposure - uncertainty factor

- An additional uncertainty factor of 10 is needed in calculating the MOEs
  - severity of the adverse effects (fetal death)
  - inadequate testing on young animals
  - carcinogenicity

Genotoxicity of MeI

MeI is clearly genotoxic:

- DNA damage: *in vivo* adduct formation (rat liver, lung, stomach and forestomach)
- Gene mutations: bacterial (*Salmonella*), mammalian (CHO cells)
- Chromosomal damage: L5178Y/TK$^{+/-}$ mouse lymphoma cells

Carcinogenicity of MeI

- MeI is likely to be a genotoxic carcinogen
  - positive genotoxicity data
  - caused astrocytoma in rat
  - caused uterine and cervical fibroma in mouse
- The thyroid follicular cell tumors found in mouse and rat may not be solely due to thyroid function perturbation

Exposure assessment

- Worker exposure estimates were calculated assuming that respirators provide 90% protection
  - effectiveness depends on proper fit and respirator maintenance
  - worker compliance may be < 100%
  - alternative exposure scenarios should be evaluated
- Tractor driver exposure estimates were calculated assuming that engineering controls provide 90% protection
  - It is not clear how 90% dilution will be achieved

Exposure assessment

- The buffer zone for non-worker by-standers (including residents) is 152 m, but the product label states “Do not apply within ¼ mile [402 m] of any occupied sensitive site”
  - residences should also be regarded as “occupied sensitive sites”