Toxicologically-based Risk Assessment for Diacetyl and 2,3-Pentanedione
Toxicologically-based Risk Assessments

• Two separate assessments
  – Toxicologically-based risk assessment for diacetyl
  – Comparative potency analysis for 2,3-pentanedione relative to diacetyl
Animal-based Diacetyl Risk Assessment

- Conducted by Dr. Bruce Allen for OSHA
- Adopted by NIOSH without modification
- **Not** the basis of the NIOSH REL
  - REL is based on human data
  - Toxicologically-based risk assessment provides supporting evidence for the REL
- Complete Allen report in criteria document
  - Will only summarize briefly here
Animal-based Diacetyl Risk Assessment

• Data from Morgan et al. 2008
  – Pilot study with 5 animals per dose group
  – Male C57Bl/6 mice
  – Inhalation study
  – 0, 25, 50, or 100 ppm
  – 6 hr/day, 5 days/week, for 6 or 12 weeks
Animal-based Diacetyl Risk Assessment

- Benchmark dose analysis
  - Multiple measures of dose considered
  - Multiple methods of extrapolating to humans

- Human dose estimates 10-100 ppb
  - Allen noted that the experimental protocol involved less than lifetime exposures
  - Should be adjusted downward for tox-based REL
  - Actual NIOSH REL is based on human data
2,3-Pentanedione Comparative Potency

- Data from Morgan et al. 2010 (abstract)
  - Individual animal data provided to NIOSH
- Inhalation study in rats and mice, M and F
- 0, 50, 100, 200 ppm 2,3-pentanedione
- 6 hr/day, 5 days/week, 2 weeks + 2 days
- 6 animals per dose group
2,3-Pentanedione Comparative Potency

• Comparing 2,3-pentanedione toxicity to diacetyl toxicity
• Diacetyl data from Morgan et al. 2008
  – Experimental study in male mice
  – Compare to mouse data for 2,3-pentanedione
• Both qualitative and quantitative comparisons
2,3-Pentanedione Comparative Potency Qualitative Comparison

• Diacetyl and 2,3-pentanedione target the same anatomical sites
  – Entire respiratory tree, from nose to lungs
  – Pathology produced by both chemicals is very similar

• Toxicities of 2,3-pentanedione and diacetyl are qualitatively similar
2,3-Pentanedione Comparative Potency Quantitative Comparison

- Benchmark dose (BMD) analysis
- Estimate BMD50 for 2,3-pentanedione and diacetyl
  - Dose at which 50% of animals are affected
  - Also referred to as median effective concentration, or EC50
- Compared mouse BMD50s to each other
  - BMD50s not extrapolated to humans
2,3-Pentanedione Comparative Potency Quantitative Comparison

• Benchmark dose analysis
• Identify endpoints where both the 2,3-pentanedione and diacetyl data are suitable for estimating BMDs
  – Need at least one partial response dose group
    • Nasal suppurative exudate in male mice
    • Bronchial inflammation – male mice for diacetyl, female mice for 2,3-pentanedione
• Compare BMD50s for 2,3-pentanedione and diacetyl
2,3-Pentanedione Comparative Potency

- Nasal Suppurative Exudate
- Bronchial Inflammation
2,3-Pentanedione Comparative Potency Quantitative Comparison

- Nasal suppurative exudate endpoint
  - 2,3-pentanedione toxicity 67-74% of diacetyl toxicity
- Bronchial inflammation endpoint
  - 2,3-pentanedione toxicity 53-58% of diacetyl toxicity
- Confidence limits broad and overlapping
- Equal potency of 2,3-pentanedione and diacetyl cannot be ruled out