

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, 5days/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

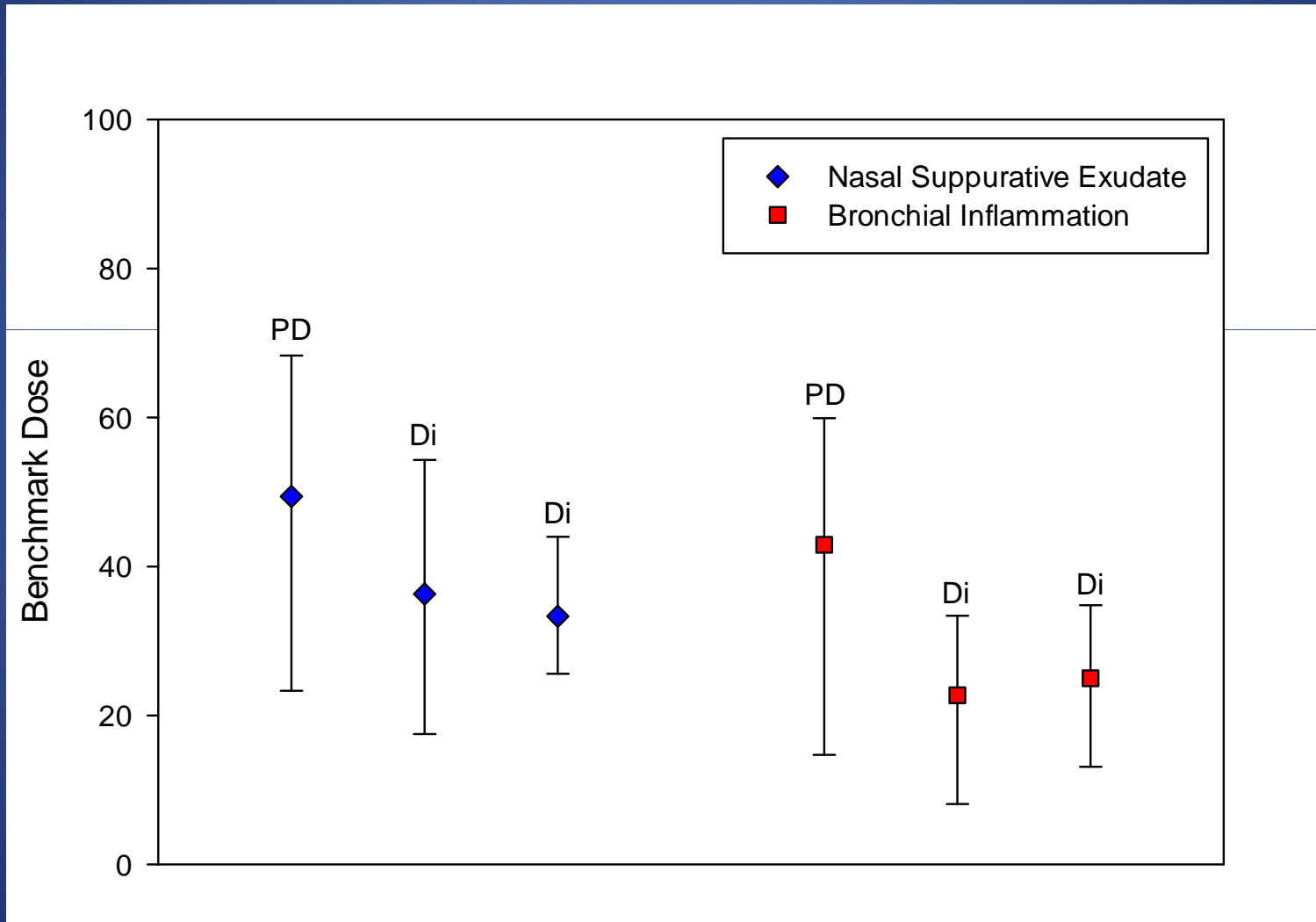
2,3-Pentanedione Comparative Potency Quantitative Comparison

- 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



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