

Peer Review of NTP Technical Reports on Dietary Zinc, 2,3-Butanedione, and p-Chloro- α,α,α -trifluorotoluene

Chad Blystone, PhD, DABT

Toxicology Branch

National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting

December 7, 2017



- NTP conducts rodent toxicity and cancer studies on agents of public health concern to identify potential hazards for human health
- NTP technical reports describe the methods, results, and NTP conclusions as “levels of evidence” for carcinogenic activity under the specific conditions of the study



Levels of Evidence of Carcinogenic Activity

Clear evidence: Dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy

Some evidence: Chemical-related increased incidence of neoplasms in which the strength of the response is less than that required for clear evidence

Equivocal evidence: Marginal increase of neoplasms that may be chemical related

No evidence: No chemical related increase in neoplasms

Inadequate study: Major limitations preclude interpretation



- Review and evaluate the scientific and technical elements of the study and its presentation
- Determine whether the study's experimental design, conduct, and results support the NTP's conclusions regarding the carcinogenic activity and toxicity of the substance tested



Technical Report Peer Review Panel

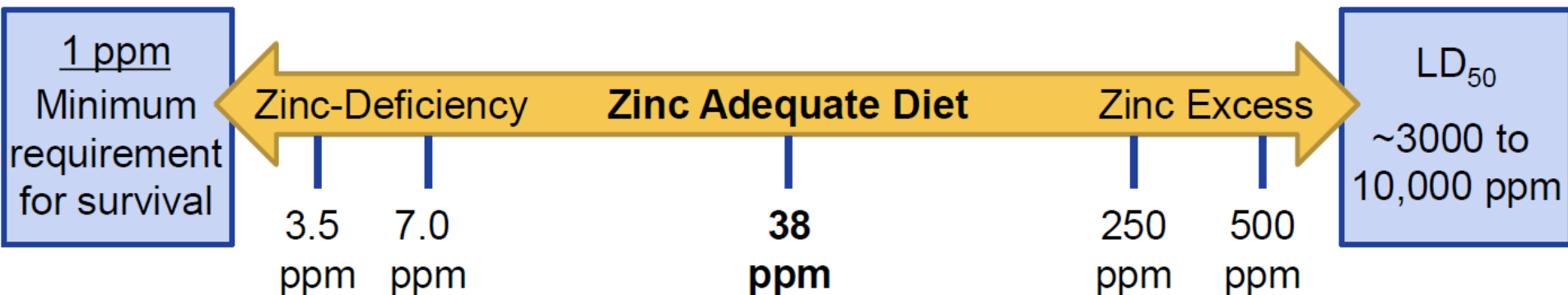
- Russell C. Cattley, VMD, PhD, DACVP, Auburn University (Panel Chair)
- Michael W. Conner, DVM, Global Bloo Therapeutics
- Noël Dybdal, DVM, PhD, DACVP, Genetech
- Terry Gordon, PhD, New York University School of Medicine
- Gabriele Ludewig, PhD, University of Iowa
- Kristini K. Miles, PhD, DABT, Kimberly-Clark Corporation
- Richard A. Peterson II, DVM, PhD, DACVP, AbbVie

- Jennifer Sass, PhD, Natural Resources Defense Council (BSC Liaison)



Draft Technical Reports Peer Reviewed

- Dietary Zinc (TR-592)
 - Used in dietary supplements
 - Deficiencies lead to disease
 - Examined effects of low and high levels of dietary zinc in Hsd:Sprague Dawley SD rats





- Diet deficient in Zinc
 - Male Rats: Equivocal evidence based on adenomas of the pancreas including multiples
 - Female Rats: No evidence of carcinogenic activity

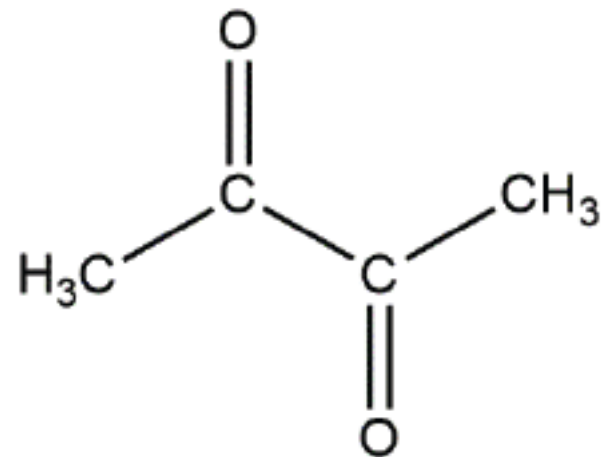
- Diet containing excess Zinc
 - Male Rats: No evidence of carcinogenic activity
 - Female Rats: No evidence of carcinogenic activity

Unanimous vote to accept



Draft Technical Reports Peer Reviewed

- 2,3-Butanedione (TR-593)
 - Used in production of artificial flavor formulations
 - Evaluated inhalation exposure in Wistar Han [CrI:WI (Han)] rats and B6C3F1/N mice





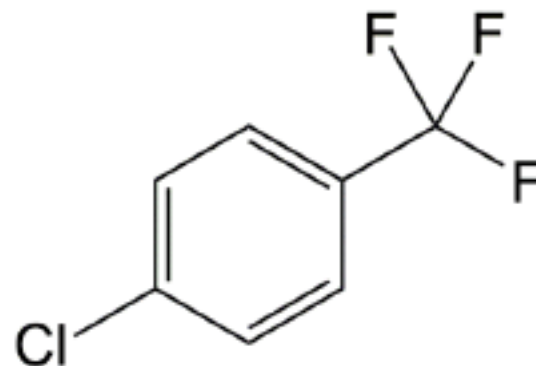
2,3-Butanedione (TR-593)

- Male Rats: Some Evidence
 - Combined incidences of squamous cell papilloma and squamous cell carcinoma of the nose
- Female Rats: Some Evidence
 - Incidences of squamous cell carcinoma of the nose
- Male Mice: No Evidence
- Female Mice: Equivocal Evidence
 - Occurrences of adenocarcinoma of the nose

Four votes approved; Two votes opposed



- p-Chloro- α,α,α -trifluorotoluene (PCTFT) (TR-594)
 - Solvent used in paints and coatings
 - Used as an industrial intermediate in chemical production
 - Evaluated inhalation exposure in Hsd:Sprague Dawley SD rats and B6C3F1/N mice





p-Chloro- α,α,α -trifluorotoluene (TR-594)

- Male Rats: Some Evidence
 - Increased incidences of C-cell adenoma in the thyroid gland
- Female Rats: Some Evidence
 - Incidences of C-cell adenoma, benign pheochromocytoma, uterine adenocarcinoma, and uterine stromal polyp
- Male Mice: Clear Evidence
 - Increased incidences of hepatocellular carcinoma and hepatoblastoma in the liver
- Female Mice: Clear Evidence
 - Increased incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma in the liver

Unanimous vote to accept



Chronic Toxicity and Carcinogenicity

- 2-Hydroxy-4-methoxybenzophenone (HMB) (TR-597)
 - Used in sunscreen and other personal care products

- Perfluorooctanoic Acid (PFOA) (TR-598)
 - Widespread “legacy” PFAS
 - Evaluated perinatal and non-perinatal exposure effects on chronic toxicity and carcinogenicity



Upcoming DART Technical Reports (2018)

Prenatal Developmental Toxicity Studies

- Tris(chloropropyl) phosphate (DART-01)
 - Used as a flame retardant
- 4-Methylcyclohexanemethanol (DART-02)
 - Used in coal purification, study part of the Elk river response
- Vinpocetine (DART-03)
 - Used as a dietary supplement
- Dimethylethanoalamine bitartrate (DART-04)
 - Used as a dietary supplement



Upcoming IMM Technical Reports (2018)

Dermal Irritancy and Hypersensitivity Study

- 4-Methylcyclohexanemethanol (IMM-01)
 - Used in coal purification
 - Study was part of the Elk River response



Upcoming TOX Technical Reports (2018)

Subchronic Toxicity Studies

- Abrasive Blasting Agents (TOX-91)
 - Used in sandblasting of various surfaces, e.g. stone buildings, ship hulls, metal bridges

- Carbon-based Nanomaterials
 - Used in industrial manufacturing
 - Fullerene C60 (TOX-87)
 - Multiwalled Carbon Nanotubes (TOX-94)

- Myristicin (TOX-95)
 - Component of nutmeg, used in essential oils and home remedies



Upcoming TOX Technical Reports (2018)

Subchronic Toxicity Studies

- Perfluorinated Alkyl Substances class study
 - Used in manufacturing to impart non-stick qualities
 - Sulfonates (TOX-96)
 - Carboxylates (TOX-97)

- Gum Guggul (TOX-98)
 - Used in dietary supplements

- Acetoin & 2,3 Pentadione (TOX-99)
 - Used in production of artificial flavoring formulations



Questions