Actions

Peer-Review Meeting of the Draft NTP Technical Reports on the Toxicology and Carcinogenesis Studies of Sodium Tungstate Dihydrate, Di-*n*-butyl Phthalate, and Di(2-ethylhexyl) Phthalate

Virtual Meeting
April 2, 2021

The National Toxicology Program (NTP) virtually convened the NTP Technical Reports Peer-Review Panel ("the Panel") on April 2, 2021, to peer review the *Draft NTP Technical Reports on the Toxicology and Carcinogenesis Studies of Sodium Tungstate Dihydrate, Di-n-butyl Phthalate, and Di(2-ethylhexyl) Phthalate*. Meeting information, including the draft reports, is currently archived under NTP's "Past Events."[1] A meeting report will be prepared and posted to the NTP website when completed.

The Panel[2] peer reviewed the draft reports and provided its opinion on NTP's preliminary conclusions regarding the level of evidence of carcinogenic activity of tungstate dihydrate, di-*n*-butyl phthalate, and di(2-ethylhexyl) phthalate. The Panel's recommendations do not necessarily represent NTP's opinion. NTP will consider the Panel's peer-review comments in finalizing the reports. When complete, the reports will be published on the NTP website.[3]

Technical Report 599: Draft NTP Technical Report on the Toxicology and Carcinogenesis Studies of Sodium Tungstate Dihydrate (CASRN 10213-10-2) in Sprague Dawley (Hsd:Sprague Dawley® SD®) Rats and B6C3F1/N Mice (Drinking Water Studies)

Male Hsd:Sprague Dawley® SD® Rats

The Panel voted to accept unanimously (5 yes, 0 no, 0 abstentions) the level of evidence conclusion as written.

- *No evidence of carcinogenic activity* at 250, 500, and 1,000 mg/L
- Exposure to sodium tungstate dihydrate in drinking water caused increased incidences of nonneoplastic lesions in the kidney of male rats.

Female Hsd:Sprague Dawley® SD® Rats

The Panel voted to accept unanimously (5 yes, 0 no, 0 abstentions) the level of evidence conclusion as written.

- *Equivocal evidence of carcinogenic activity*
  - Increased incidences of C-cell adenoma or carcinoma (combined) of the thyroid gland.
- Exposure to sodium tungstate dihydrate in drinking water caused increased incidences of nonneoplastic lesions in the kidney and uterus of female rats.

[1] https://ntp.niehs.nih.gov/go/meeting
[2] https://ntp.niehs.nih.gov/ntp/about_ntp/trpanel/2021/april/rostertrprp20210402_508.pdf
[3] https://ntp.niehs.nih.gov/go/750897

Male B6C3F1/N Mice

The Panel voted to accept unanimously (5 yes, 0 no, 0 abstentions) the level of evidence conclusion as written.

- *Equivocal evidence of carcinogenic activity*
  - Occurrences of renal tubule adenoma or carcinoma (combined) in exposed animals.
- Exposure to sodium tungstate dihydrate in drinking water caused increased incidences of nonneoplastic lesions in the kidney, testes, and bone marrow of male mice.

Female B6C3F1/N Mice

The Panel voted to accept unanimously (5 yes, 0 no, 0 abstentions) the level of evidence conclusion as written.

- *No evidence of carcinogenic activity* at 500, 1,000, and 2,000 mg/L.
- Exposure to sodium tungstate dihydrate in drinking water caused increased incidences of nonneoplastic lesions in the kidney and spleen of female mice.

Technical Report 600: Draft NTP Technical Report on the Toxicology and Carcinogenesis Studies of Di-*n*-butyl Phthalate (CASRN 84-74-2) Administered in Feed to Sprague Dawley (Hsd:Sprague Dawley® SD®) Rats and B6C3F1/N Mice

Male Hsd:Sprague Dawley® SD® Rats

The Panel voted to accept unanimously (5 yes, 0 no, 0 abstentions) the level of evidence conclusion as written.

- *Equivocal evidence of carcinogenic activity*
  - Marginal increases in the incidence of pancreatic acinus adenomas.
- Exposure to di-*n*-butyl phthalate resulted in increased incidences of gross lesions of the male reproductive system and nonneoplastic lesions of the male reproductive system, liver, and pituitary gland pars distalis in male rats.

Female Hsd:Sprague Dawley® SD® Rats

The Panel voted to accept unanimously (5 yes, 0 no, 0 abstentions) the level of evidence conclusion as written.

- *No evidence of carcinogenic activity* at 300, 1,000, 3,000, or 10,000 ppm.
- Exposure to di-*n*-butyl phthalate resulted in increased incidences of nonneoplastic lesions of the liver in female rats.

Male B6C3F1/N Mice

The Panel voted to accept unanimously (5 yes, 0 no, 0 abstentions) the level of evidence conclusion as written.

- *No evidence of carcinogenic activity* at 1,000, 3,000, or 10,000 ppm.
- Exposure to di-*n*-butyl phthalate resulted in increased incidences of nonneoplastic lesions of the male reproductive system and liver in male mice.

Female B6C3F1/N Mice

The Panel voted to accept unanimously (5 yes, 0 no, 0 abstentions) the level of evidence conclusion as written.

- *No evidence of carcinogenic activity* at 1,000, 3,000, or 10,000 ppm.
- Exposure to di-*n*-butyl phthalate resulted in increased incidences of nonneoplastic lesions of the liver and kidney in female mice.

Technical Report 601: Draft NTP Technical Report on the Toxicology and Carcinogenesis Studies of Di(2-ethylhexyl) Phthalate (CASRN 117-81-7) Administered in Feed to Sprague Dawley (Hsd:Sprague Dawley® SD®) Rats

Perinatal and Postweaning Feed Study

Male Hsd:Sprague Dawley® SD® Rats

The Panel voted to accept unanimously (5 yes, 0 no, 0 abstentions) the level of evidence conclusion as written.

- *Clear evidence of carcinogenic activity*
  - Increased incidences of hepatocellular adenoma or carcinoma (combined).
  - Increased incidences of acinar adenoma or carcinoma (combined) neoplasms (predominantly adenomas) of the pancreas.
- Exposure to di(2-ethylhexyl) phthalate resulted in increased incidences of nonneoplastic lesions in the liver, heart, pituitary gland, testis, and epididymis and increased incidences of gross lesions in the reproductive tract, bone marrow, and kidney in male rats.

Female Hsd:Sprague Dawley® SD® Rats

The Panel voted to accept unanimously (5 yes, 0 no, 0 abstentions) the level of evidence conclusion with the following marked changes.

- *Clear evidence of carcinogenic activity*
  - Increased incidence of hepatocellular adenoma or carcinoma (combined).
- The occurrence of pancreatic acinar adenoma or carcinoma (combined) was considered to be related to exposure. (*Some evidence*)
- The occurrence of uterine (including cervix) adenoma, adenocarcinoma, squamous cell carcinoma, or squamous cell papilloma (combined) in female rats may have been related to exposure. (*Equivocal evidence*)
- Exposure to di(2-ethylhexyl) phthalate resulted in increased incidences of nonneoplastic lesions in the liver, ~~and increased incidences of gross lesions of the~~ kidney, and uterus in female rats~~.~~ and gross observations in the female reproductive tract.

Postweaning-only Study

Male Hsd:Sprague Dawley® SD® Rats

The Panel voted to accept unanimously (5 yes, 0 no, 0 abstentions) the level of evidence conclusion as written.

- *Clear evidence of carcinogenic activity*
  - Increased incidences of hepatocellular adenoma or carcinoma (combined).
  - Increased incidences of acinar adenoma or carcinoma (combined) neoplasms (predominantly adenomas) of the pancreas.
- The occurrence of testicular interstitial cell adenoma in male rats may have been related to exposure. (*Equivocal evidence*)
- Exposure to di(2-ethylhexyl) phthalate resulted in increased incidences of nonneoplastic lesions in the liver, pancreas, bone marrow, heart, pituitary gland, testis, and epididymis.

Female Hsd:Sprague Dawley® SD® Rats

The Panel voted to accept unanimously (5 yes, 0 no, 0 abstentions) the level of evidence conclusion with the following marked changes.

- *Clear evidence of carcinogenic activity*
    - Increased incidences of hepatocellular adenoma or carcinoma (combined) and uterine (including cervix) adenoma, adenocarcinoma, squamous cell carcinoma, or squamous cell papilloma (combined).
- The occurrence of pancreatic acinar adenoma or carcinoma (combined) in female rats was considered to be related to exposure. (*Some evidence*)
- Exposure to di(2-ethylhexyl) phthalate resulted in increased incidences of nonneoplastic lesions in the liver, pancreas, ~~bone marrow,~~ and uterus in female rats.

Comparative Carcinogenic Benchmark Dose Analyses

Hsd:Sprague Dawley® SD® Rats

The Panel voted to accept unanimously (5 yes, 0 no, 0 abstentions) the conclusion as written.

- No consistent pattern indicating that perinatal and postweaning exposure was more sensitive compared to postweaning-only exposure and modeled responses were within threefold of each other.
- However, there was a stronger carcinogenic response in the reproductive organs (uterus and testis) in the postweaning-only exposure study compared to the perinatal and postweaning exposure study.