NTP
National Toxicology Program

Draft NTP Technical Report TR-580 on β-Picoline

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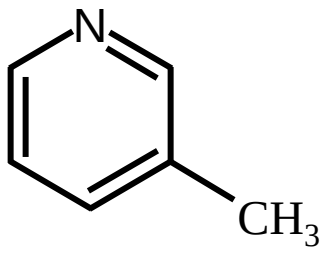
Background

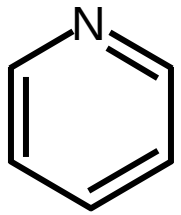
- Nominated by NIEHS for toxicity and carcinogenicity testing based on its high U.S. production volume and potential for human exposure
- Used as a solvent, as a laboratory reagent, and intermediate in the manufacture of insecticides, waterproofing agents, niacin, and niacinamide.
- Released into environment via wastewater effluents
- Exposure to general population primarily occurs via contaminated drinking water

Toxicology

- Reduced appetite and activity, acute gastrointestinal inflammation, hemorrhagic lungs, liver discoloration, slight growth inhibition, and fatty liver in acute studies
- Negative in mutagenicity assays
  - *Salmonella* and micronucleus
- *β*-Picoline is a structural derivative of pyridine



β-Picoline



Pyridine

TR-470 (1997)

Subchronic Studies – Rats

- Fischer 344/N rats were administered *β*-picoline in drinking water 0, 78, 156, 312, 625, or 1250 mg/L for 13 weeks
- Decreased terminal group mean body weights and reduced water consumption relative to control in both sexes at ≥625 mg/L
  - Reduced WC attributed to an aversion to the palatablility of *β*-picoline at both concentrations

Subchronic Studies – Rats

- Concentration of renal *α*2u-globulin significantly increased at ≥ 312 mg/L in males
- Increased severity of chronic progressive nephropathy and hyaline droplet accumulation in proximal renal tubules in males
- Kidney lesions were consistent with *α*2u-globulin nephropathy
- In females, there was a increasing trend in the incidence of mineralization of the renal medulla

Subchronic Studies – Mice

- Male and female B6C3F1 mice were administered *β*-picoline in drinking water at 0, 78, 156, 312, 625, or 1250 mg/L for 13 weeks
- No significant treatment-related effects on clinical observations, survival, body weight, organ weights, clinical pathology, water consumption, gross or microscopic lesions

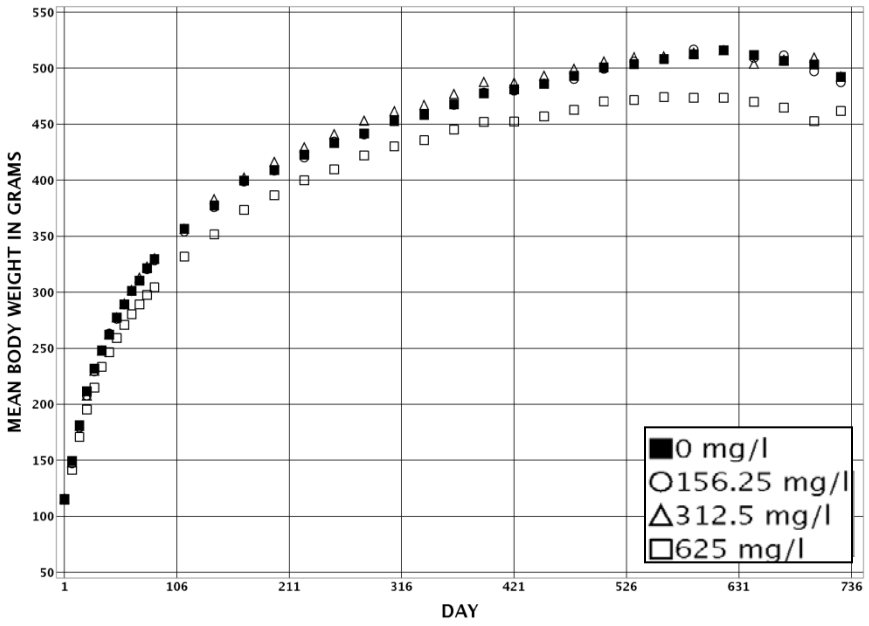
Dose Selection Rationale

- Results were similar to those for the structural-derivative pyridine, however *β*-picoline exposure did not elicit liver effects, or as broad a spectrum or profound a response in the kidney in rats
- Based on subchronic results, the chronic administered exposures for *β*-picoline in dosed-water were:
  - Male and female F344/N rats at 0, 156.25, 312.5, 625 mg/L
  - Male and female B6C3F1 mice at 0, 312.5, 625, or 1250 mg/L

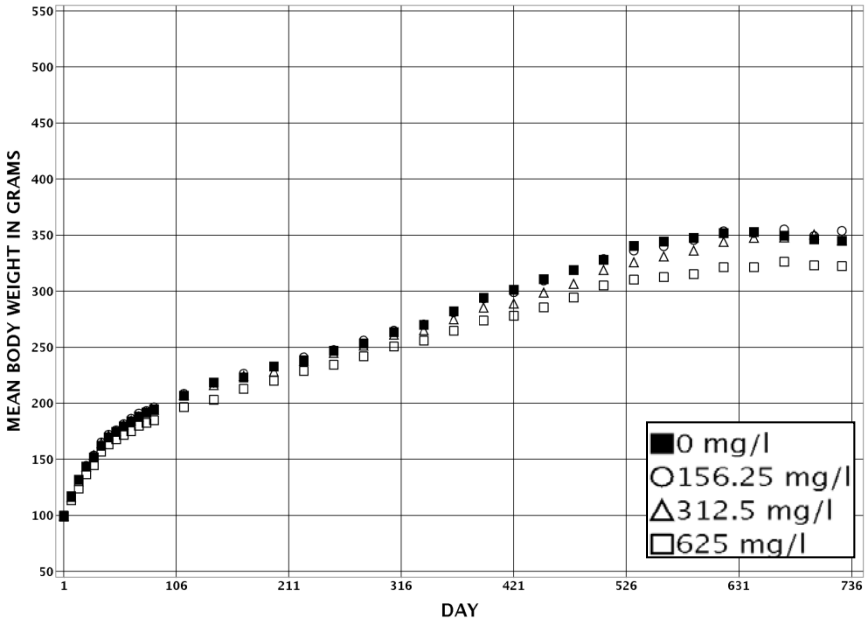
Chronic Rat Study Results

- No treatment-related effect on survival
- Slight decrease in body weight at 625 mg/L (↓6-10%)

Males



Females



Alveolar/Bronchiolar Neoplasms

mg/l	0	156.25	312.5	625
Female Rats				
Alveolar/bronchiolar adenoma[a]	0*	3	2	5*
Alveolar/bronchiolar carcinoma[b]	0	1	0	0
Alveolar/bronchiolar adenoma or carcinoma[c]	0*	4	2	5*

* $P \leq 0.05$

[a] Historical incidence: 4/100 (0-8% drinking water), 25/1200 (0-8% all routes)

[b] Historical incidence: 0/100 (drinking water), 3/1200 (0-2% all routes)

[c] Historical incidence: 4/100 (0-8%, drinking water), 27/1200 (0-8% all routes)

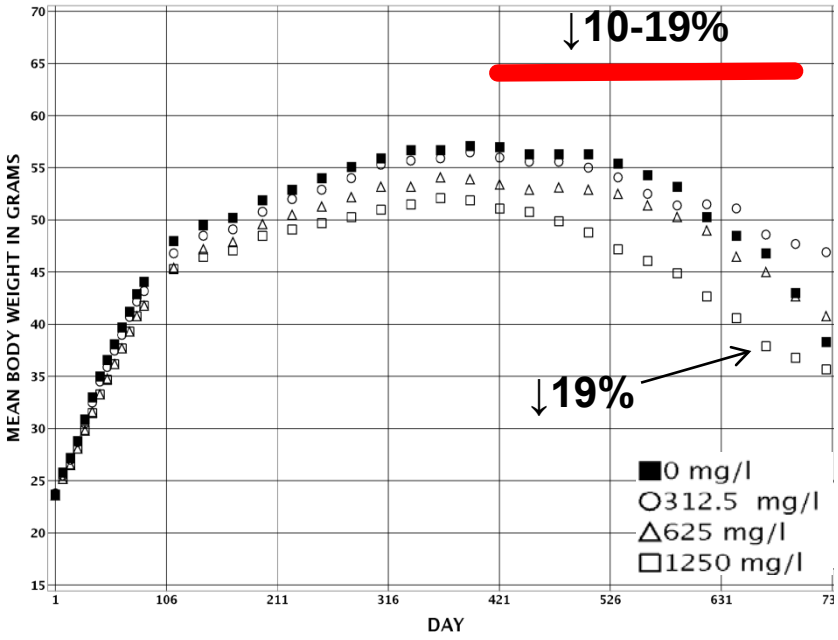
Non-neoplastic lung lesions

mg/l	0	156.25	312.5	625
Female Rats				
Alveolar epithelium hyperplasia	7	14	14	11
Alveolar epithelium squamous metaplasia	0	3	1	1

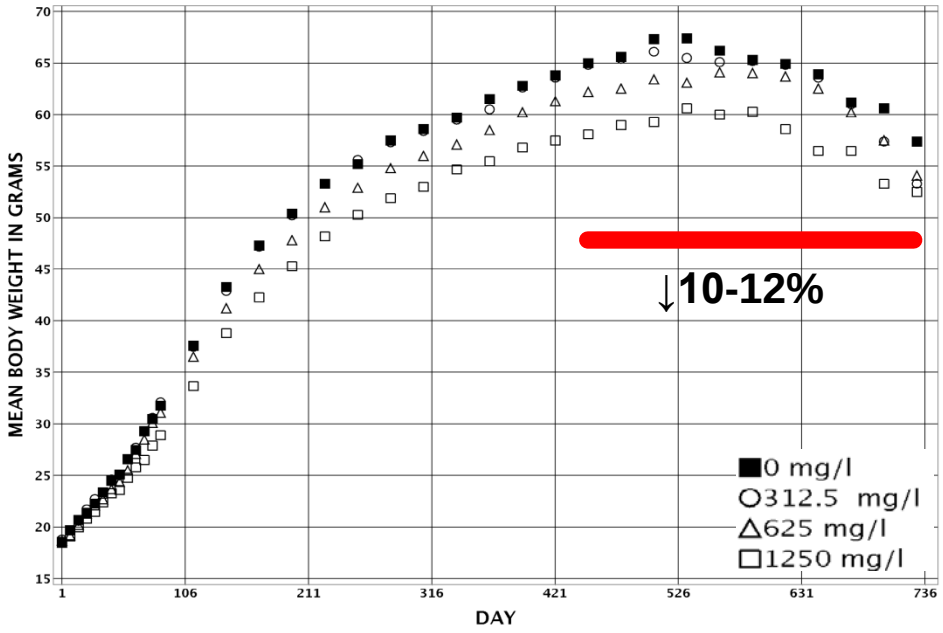
Chronic Mouse Study Results

- Slightly positive trend in the survival of males (48, 52, 54, 66%), no treatment-related effect on survival in females
- Decreased body weight at 1250 mg/L

Males



Females



Alveolar/Bronchiolar Neoplasms

mg/l	0	312.5	625	1250
Male Mice				
Alveolar/bronchiolar adenoma[a]	6	11	16*	8
Adenoma, multiple	0	0	2	2
Alveolar/bronchiolar carcinoma[b]	9	9	8	9
Carcinoma, multiple	0	2	0	3
Alveolar/bronchiolar adenoma or carcinoma[c]	14	19	21	15

* $P < 0.05$

[a] Historical incidence: 21/100 (12-30%, drinking water), 172/1150 (2-30% all routes)

[b] Historical incidence: 12/100 (6-18%, drinking water), 144/1150 (4-24% all routes)

[c] Historical incidence: 30/100 (28-32%, drinking water), 301/1150 (14-40% all routes)

Alveolar/Bronchiolar Neoplasms

mg/l	0	312.5	625	1250
Female Mice				
Alveolar/bronchiolar adenoma[a]	5*	6	4	11
Adenoma, multiple	0	1	0	1
Alveolar/bronchiolar carcinoma[b]	7	8	10	13
Carcinoma, multiple	0	2	2	4
Alveolar/bronchiolar adenoma or carcinoma[c]	11*	13	13	21*

* $P < 0.05$
[a] Historical incidence: 6/100 (2-10%, drinking water), 60/1196 (0-12% all routes)
[b] Historical incidence: 9/100 (4-14%, drinking water), 44/1196 (0-14% all routes)
[c] Historical incidence: 13/100 (4-22%, drinking water), 100/1196 (2-22% all routes)

Non-neoplastic lung lesions

mg/l	0	312.5	625	1250
Male Mice				
Alveolar epithelium hyperplasia	4	6	6	7
Female Mice				
Alveolar epithelium hyperplasia	2	4	3	8*
Bronchiole hyperplasia	0	0	3	1

* $P < 0.05$

Liver Neoplasms

mg/l	0	312.5	625	1250
Female Mice				
Hepatocellular adenoma[a]	38	46*	46	39
Hepatocellular carcinoma[b]	11**	20*	26**	23**
Hepatoblastoma[c]	1	3	4	4
Hepatoblastoma or carcinoma[d]	12**	21*	28**	24**

* $P < 0.05$; ** $P < 0.01$
[a] Historical incidence: 52/98 (29-78%, drinking water), 380/1195 (2-78% all routes)
[b] Historical incidence: 19/98 (16-22%, drinking water), 144/1195 (0-46% all routes)
[c] Historical incidence: 1/98 (0-2%, drinking water), 4/1195 (0-2% all routes)
[d] Historical incidence: 20/98 (16-24%, drinking water), 148/1195 (0-46% all routes)

Non-neoplastic lesions of the nose

mg/l	0	312.5	625	1250
Male Mice				
Olfactory epithelium atrophy	3	4	8	7
Olfactory epithelium respiratory metaplasia	8	12	30**	41**
Female Mice				
Olfactory epithelium atrophy	1	2	2	7*
Olfactory epithelium respiratory metaplasia	2	2	7	14**

Conclusions for Carcinogenic Activity

- Male F344/N rats
  - ***No evidence***
- Female F344/N rats
  - ***Some evidence*** based on incidences of alveolar/bronchiolar adenomas and combined incidences of alveolar/bronchiolar adenomas and carcinomas
- Male B3C6F1 mice
  - ***Equivocal evidence*** based on incidences of alveolar/bronchiolar adenomas and combined incidences of A/B adenomas and carcinomas
- Female B3C6F1 mice
  - ***Clear evidence*** based on the combined incidences of alveolar/bronchiolar adenomas and carcinomas in the lung and hepatocellular carcinoma and hepatoblastoma in the liver