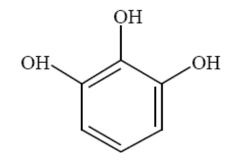
# Draft NTP Technical Report TR574 on **Pyrogallol**

Minerva Mercado-Feliciano, Ph.D., DABT National Institute of Environmental Health Sciences

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## Pyrogallol – Background



- Natural decomposition by-product of plant tannins
  - Soil, tea, smoked fish/meat, tobacco smoke, industrial waste (sawmills, instant coffee, rubber, coal)
- Use in manufacture and consumer products
  - Dyes: hair, fur, wool, leather, surgery sutures
  - Corrosion inhibitor: boilers, semiconductor, microchips
  - Fine arts photographic developer
  - Historic use as topical antipsoriatic (2%-10%)



## **Pyrogallol – Nomination**

- By private individuals
- Frequent occurrence in natural and manufactured products, including hair dyes
- Lack of carcinogenicity data

## Pyrogallol – Study Design

- Genetic toxicity studies (in vitro and in vivo)
- Contact hypersensitivity
- 90-day studies
- 2-year studies
- Dermal route
  - Occupational dermal exposure is the most common route in humans

## **Pyrogallol – Genetic Toxicity Studies**

- Bacterial gene mutation tests (in vitro)
  - With metabolic activation: positive in 3 strains
  - Without metabolic activation:
    - Equivocal in two S. typhimurium strains
    - Positive in one E. coli strain

- B6C3F1/N mice micronucleus test
  - 90-day dermal (peripheral blood erythrocytes)
    - Equivocal in males, negative in females
  - 3-day intraperitoneal (bone marrow reticulocytes)
    - Negative in males

## Pyrogallol – Contact Hypersensitivity Study

- 0, 0.125%, 0.25%, 0.5%, 1.0%, 2.5%, 5%, 10%, 25% and 50% w/v
  - Female BALB/c mice

- Findings:
  - Weak Sensitizer
    - Positive at 0.5% in Local Lymph Node Assay
    - Negative in Mouse Ear Swelling Test
  - Strong Irritant at all doses

## Pyrogallol – 90-Day Dermal Studies

- 5 doses at max concentration
  - F344/N rats: 0, 9.5, 18.75, 37.5, 75, 150 mg/kg
  - B6C3F1/N mice: 0, 38, 75, 150, 300, 600 mg/kg

### Findings:

- All animals survived, no significant changes in body weight
- Site of application irritation, inflammation, hyperkeratosis and hyperplasia - Both species and at all doses
- Low incidence of site of application ulcers (≥ 150 mg/kg)



## Rat – 90-Day Non-neoplastic SOA Lesions

Dose (mg/kg)	0	9.5	18.75	37.5	75	150
F344/N Males N	10	10	10	10	10	10
Squamous Hyperplasia	1 (1.0)	10** (1.0)	10** (1.0)	10** (1.0)	10** (1.5)	10** (1.4)
Hyperkeratosis	0	10** (1.1)	10** (1.3)	10** (1.7)	10** (2.2)	10** (2.0)
Inflammation, Chronic	0	9** (1.1)	9** (1.2)	10** (1.0)	10** (1.8)	10** (1.9)
Ulcer	0	0	0	0	0	1 (2.0)
F344/N Females N	10	10	10	10	10	10
Squamous Hyperplasia	0	10** (1.0)	10** (1.0)	10** (1.0)	10** (1.3)	10** (1.1)
Hyperkeratosis	0	10** (1.0)	10** (1.4)	10** (1.4)	10** (1.9)	10** (2.1)
Inflammation, Chronic	0	8** (1.0)	10** (1.5)	9** (1.8)	10** (2.0)	10** (1.8)

<sup>\*\*</sup> Significantly different (P≤0.01) from vehicle control group by Fisher exact test Average severity grade of lesion in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

## Pyrogallol – 2-Year Dermal Studies

0, 5, 20, 75 mg/kg rats and mice

#### Dose rationale:

- Doses ≥ 150 mg/kg were too high for a 2-year study due to the increase in the severity of chronic active inflammation and the presence of ulcers.
- Use of 38 mg/kg was discussed but upon pathology review of the skin lesions, 75 mg/kg was selected as a sufficiently challenging high dose for a 2-year study.
- Lesions were seen as low as 10 mg/kg, therefore 5 mg/kg was selected as the lowest dose for the 2-year study.

## Pyrogallol – 2-Year Dermal Studies

- 0, 5, 20, 75 mg/kg rats and mice
- Findings:
  - Survival and body weights of treated rats and male mice not different from controls
  - Decreased survival and weight gain in 75 mg/kg female mice
  - Non-neoplastic lesions at application site, same as 13-week
    - Both species
    - At all doses for most lesions
    - Mice had more types of lesions than rats (sebaceous gland hyperplasia, fibrosis, pigmentation), and outside app. site
    - Mammary gland hyperplasia in 75 mg/kg female mice
  - Treatment-related site of application tumors in mice (not in rats)



## Mice – 2-yr Study SOA Tumors

Dose (mg/kg)		0	5	20	75
B6C3F1/N Males	N	50	50	50	50
Squamous Cell Papilloma		0*	0	0	2 (4%)
Historical Controls		same route/vehicle: all routes/vehicles:			0/200 (0%) 1/1150 (0.1%)
B6C3F1/N Females	N	50	50	50	50
Squamous Cell Carcinoma		0***	0	0	4* (8%)
Historical Controls		same route/vehicle: all routes/vehicles:			1/348 (0.3%) 1/1198 (0.2%)

## **Pyrogallol – Conclusions**

- Under the conditions of these 2-year dermal studies, there was:
  - No evidence of carcinogenic activity of pyrogallol in male or female F344/N rats administered 5, 20, or 75 mg/kg.
  - There was equivocal evidence of carcinogenic activity of pyrogallol in male B6C3F1/N mice based on increased incidences of squamous cell papilloma of the skin at the site of application.
  - There was some evidence of carcinogenic activity of pyrogallol in female B6C3F1/N mice based on increased incidences of squamous cell carcinoma of the skin at the site of application.
  - Dermal administration of pyrogallol caused increased incidences of nonneoplastic lesions of the skin at the site of application in male and female rats and mice; skin adjacent to the site of application in male and female mice; and mammary gland in female mice.