



**NTP**

National Toxicology Program

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# Sodium Bromate

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- Drinking water DBP formed during the ozonation of source water containing bromide

- Used by the cosmetic industry as a neutralizer or oxidizer in hair wave preparations



# DBP Selection

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## Dichloroacetic acid (DCA)

DCA is well studied rodent liver carcinogen

Representative haloacetic acid second most common DBP

Weakly mutagenic

## Bromodichloromethane (BDCM)

BDCM is well studied rodent carcinogen (colon, kidney - rats, kidney - male mice, liver - female mice).

Representative trihalomethane

Mutagenic in bacterial systems, does not induce micronuclei

## Bromate

Common anion found after ozonation of water

Well studied renal carcinogen in rodents, mutagenic

# Study Design

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## ◆ Dermal studies

- Male and female Tg.AC hemizygous mice
- 26- and 39-week studies (N=15, 10)
- Dose groups- vehicle control, 64, 128, or 256 mg/kg

## ◆ Drinking water studies

- Male and female Tg.AC hemizygous mice and p53 haploinsufficient mice
- 27- and 43-week studies (N=15, 10)
- Concentrations- 0, 80, 400, or 800 mg/L

# Results of Dermal Studies in Tg.AC Mice

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- ◆ **Survival was similar to controls**
- ◆ **Mean body weights decreased**
  - 256 mg/kg males in both studies
  - All dosed groups of females at 39 weeks
- ◆ **Minimal changes in hematology**
  - Decreased erythron (hematocrit, hemoglobin, erythrocytes)
  - Increased reticulocyte counts
- ◆ **No treatment-related neoplasms**

# Nonneoplastic Lesions in the Kidney

Dose (mg/kg )	0	64	128	256
<b><u>Male</u></b>				
Nephropathy				
26-week <sup>a</sup>	53% (1.0) <sup>c</sup>	53% (1.1)	93%* (1.0)	93%* (1.1)
39-week <sup>b</sup>	70% (1.0)	100% (1.1)	90% (1.1)	100% (1.2)
<b><u>Female</u></b>				
Nephropathy				
26-week <sup>a</sup>	53% (1.0)	47% (1.0)	87% (1.0)	100%** (1.0)
39-week <sup>b</sup>	56% (1.0)	60% (1.0)	80% (1.0)	100%* (1.3)

<sup>a</sup>N=15

<sup>b</sup>N=10; except control females, N=9

<sup>c</sup>Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

\*P ≤ 0.05

\*\*P ≤ 0.01

# Nonneoplastic Lesions in the Thyroid

Dose (mg/kg )	0	64	128	256
<b>Male</b>				
Hypertrophy				
26 -week <sup>a</sup>	0	47%** (1.0) <sup>c</sup>	67%** (1.3)	93%** (1.4)
39 -week <sup>b</sup>	0	90%** (1.0)	80%** (1.5)	80%** (1.9)
<b>Female</b>				
Hypertrophy				
26 -week <sup>a</sup>	7% (1.0)	60%** (1.0)	80%** (1.9)	87%** (2.8)
39 -week <sup>b</sup>	11% (1.0)	90%** (1.6)	90%** (2.9)	100%** (3.3)
Secretory Depletion				
26 -week <sup>a</sup>	40% (1.2)	73% (1.2)	87%** (1.5)	93%** (2.6)
39 -week <sup>b</sup>	56% (1.2)	80% (1.5)	100%* (2.7)	100%* (3.5)
Lymphocyte Infiltration				
26 -week <sup>a</sup>	0	40%** (1.0)	20% (1.0)	80%** (1.3)
39 -week <sup>b</sup>	0	20% (1.5)	50%* (1.2)	100%** (1.4)

<sup>a</sup>N=15

<sup>b</sup>N=10; except control females, N=9

<sup>c</sup>Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

\*P≤0.05

\*\*P≤0.01

# Results of DW Studies in Tg.AC Mice

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- ◆ **Survival was similar to controls at 27 weeks**
  - Decreased in 400 mg/L females and 800 mg/L males and females at 43 weeks
- ◆ **Mean body weights were decreased in 400 mg/L males and 800 mg/L males and females**
- ◆ **Water consumption was similar to controls**
- ◆ **Minimal changes in hematology**
  - Decreased erythron (hematocrit, hemoglobin, erythrocytes)
  - Increased reticulocyte counts
- ◆ **No treatment-related neoplasms**

# Nonneoplastic Kidney Lesions in Males

Concentration (mg/L)	0	80	400	800
Nephropathy				
27-week <sup>a</sup>	7% (1.0) <sup>c</sup>	47%* (1.0)	67%** (1.0)	93%** (1.6)
43-week <sup>b</sup>	70% (1.0)	60% (1.3)	70% (1.3)	100% (1.8)
Renal Tubule Degeneration				
27-week <sup>a</sup>	0	0	0	67%** (1.3)
43-week <sup>b</sup>	0	0	10% (3.0)	80%** (3.0)
Renal Tubule Hypertrophy				
27-week <sup>a</sup>	0	0	0	13% (1.0)
43-week <sup>b</sup>	0	0	10% (1.0)	60%** (1.3)

<sup>a</sup>N=15

<sup>b</sup>N=10

<sup>c</sup>Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

\*P≤0.05

\*\*P≤0.01

# Nonneoplastic Kidney Lesions in Females

Concentration (mg/L)	0	80	400	800
<b>Nephropathy</b>				
27-week <sup>a</sup>	13% (1.0) <sup>c</sup>	13% (1.0)	67%** (1.0)	87%** (1.8)
43-week <sup>b</sup>	60% (1.0)	60% (1.0)	80% (1.3)	80% (1.3)
<b>Renal Tubule Degeneration</b>				
27-week <sup>a</sup>	0	0	13% (1.0)	53%** (1.9)
43-week <sup>b</sup>	0	0	0	70%** (2.3)
<b>Renal Tubule Hypertrophy</b>				
27-week <sup>a</sup>	0	7% (1.0)	33%* (1.0)	80%** (1.8)
43-week <sup>b</sup>	0	0	20% (1.0)	50%* (1.6)

<sup>a</sup>N=15

<sup>b</sup>N=10

<sup>c</sup>Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

\*P≤0.05

\*\*P≤0.01

# Nonneoplastic Thyroid Lesions- Males

Concentration (mg/L )	0	80	400	800
<b>Hypertrophy</b>				
27-week <sup>a</sup>	7% (2.0) <sup>c</sup>	14% (1.5)	80%** (1.6)	100%** (2.0)
43-week <sup>b</sup>	0	60%** (1.0)	80%** (2.0)	89%** (3.5)
<b>Secretory Depletion</b>				
27-week <sup>a</sup>	27% (1.0)	43% (1.0)	100%** (1.1)	100%** (1.3)
43-week <sup>b</sup>	30% (1.0)	40% (1.0)	40% (1.5)	78% (3.7)
<b>Lymphocyte Infiltration</b>				
27-week <sup>a</sup>	0	7% (1.0)	7% (1.0)	13% (1.0)
43-week <sup>b</sup>	0	0	0	44%* (1.8)

<sup>a</sup>N=15; except 80 mg/L , N=14

<sup>b</sup>N=10; except 800 mg/L , N=9

<sup>c</sup>Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

\*P≤0.05

\*\*P≤0.01

# Nonneoplastic Thyroid Lesions- Females

Concentration (mg/L )	0	80	400	800
<b>Hypertrophy</b>				
27-week <sup>a</sup>	13% (1.0) <sup>c</sup>	15% (1.0)	85%** (1.9)	87%** (3.2 )
43-week <sup>b</sup>	0	89%** (1.0 )	100%** (2.6 )	100%** (3.3)
<b>Secretory Depletion</b>				
27-week <sup>a</sup>	47% (1.1 )	54% (1.6 )	85%* (1.8 )	93%** (3.1 )
43-week <sup>b</sup>	10% (2.0 )	89%** (1.3)	90%** (3.0 )	100%** (3.3)
<b>Lymphocyte Infiltration</b>				
27-week <sup>a</sup>	0	0	38%* (1.0)	73%** (1.5 )
43-week <sup>b</sup>	0	22% (1.0 )	70%** (1.1)	80%** (1.4)

<sup>a</sup>N=15; except 80 and 400 mg/L, N=13

<sup>b</sup>N=10; except 80 mg/L, N=9

<sup>c</sup>Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

\*P ≤ 0.05

\*\*P ≤ 0.01

# Additional Nonneoplastic Lesions

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- ◆ Pituitary gland pars distalis hypertrophy
- ◆ Degeneration of the testes/epididymis
- ◆ Hematopoietic cell proliferation
- ◆ Forestomach epithelial hyperkeratosis

## Conclusions- Tg.AC Mice

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- ◆ **No treatment-related neoplasms were seen in male or female Tg.AC hemizygous mice exposed**
  - **dermally to 64, 128, or 256 mg sodium bromate/kg body weight for 26 or 39 weeks.**
  - **by drinking water to 80, 400, or 800 mg sodium bromate/L for 27 or 43 weeks.**
  
- ◆ **Increased incidences of nonneoplastic lesions in the thyroid gland and kidney.**

## Results of DW Studies in p53 Mice

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- ◆ 27- and 43-week studies
- ◆ Survival was similar to controls
- ◆ Mean body weights were decreased in females exposed to 400 and 800 mg/L
- ◆ Water consumption was similar to controls
- ◆ No neoplasms or nonneoplastic lesions in males or females attributed to Na bromate exposure

## Conclusions- p53 Mice

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- ◆ Under the conditions of these drinking water studies, there was *no evidence of carcinogenic activity* of sodium bromate in male or female p53 haploinsufficient mice exposed to 80, 400, or 800 mg/L for 27 or 43 weeks.

# Utility of GMM Models for Na Bromate

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- ◆ **The p53 haploinsufficient mouse was not responsive to sodium bromate exposure even though sodium bromate is genotoxic.**
- ◆ **Sodium bromate is a known rodent carcinogen but no neoplastic lesions were attributed to exposure in Tg.AC and p53 mice.**
- ◆ **These models do not provide a sensitive and rapid means of assessing potential toxicity and carcinogenicity of sodium bromate.**



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# **NTP Technical Reports Review Subcommittee Meeting**

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## **Sodium Bromate GMM 6**

