NTP
National Toxicology Program

Draft NTP Technical Report 588 on
Glycidamide in Drinking Water

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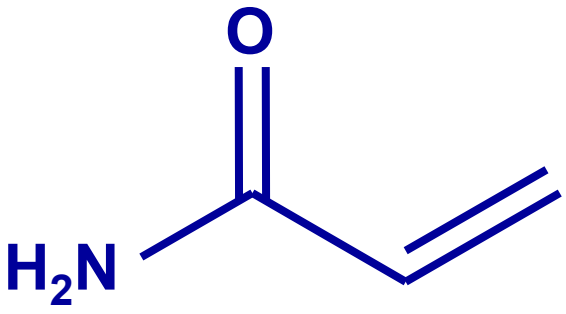
ACRYLAMIDE



- High-production chemical (>200 Gg/yr)
- Polymeric forms used in water treatment, crude oil and pulp-paper processing, concrete and grouts
- Monomeric acrylamide used for PAGE
- Cigarette smoke (3.1 µg/kg bw/day)
- Food (French fries, potato chips, bread, cereals, coffee; 0.44 µg/kg bw/day)

STUDY RATIONALE

- Acrylamide was nominated by the Center for Food Safety and Applied Nutrition, FDA, for an in-depth toxicological evaluation
- Acrylamide is present in certain baked and fried starchy foods
- Better dose-response data are needed to develop risk estimates (*e.g.* 2 species)
- Mechanism of acrylamide carcinogenicity is uncertain

METABOLISM OF ACRYLAMIDE

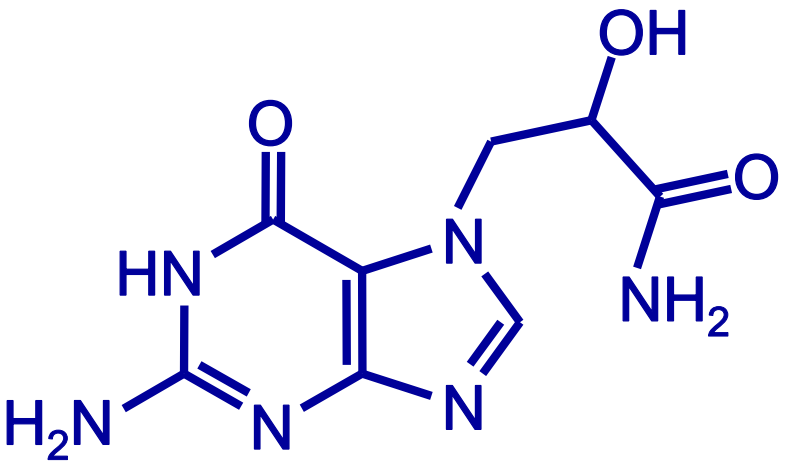
Acrylamide

Glycidamide

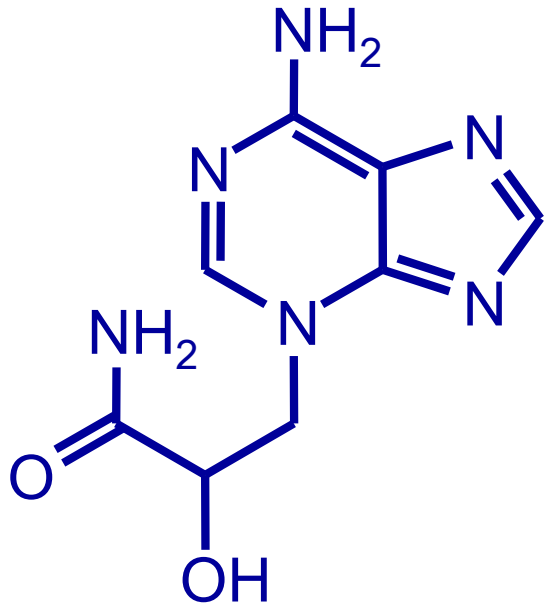
DNA

DNA adducts

GLYCIDAMIDE DNA ADDUCTS

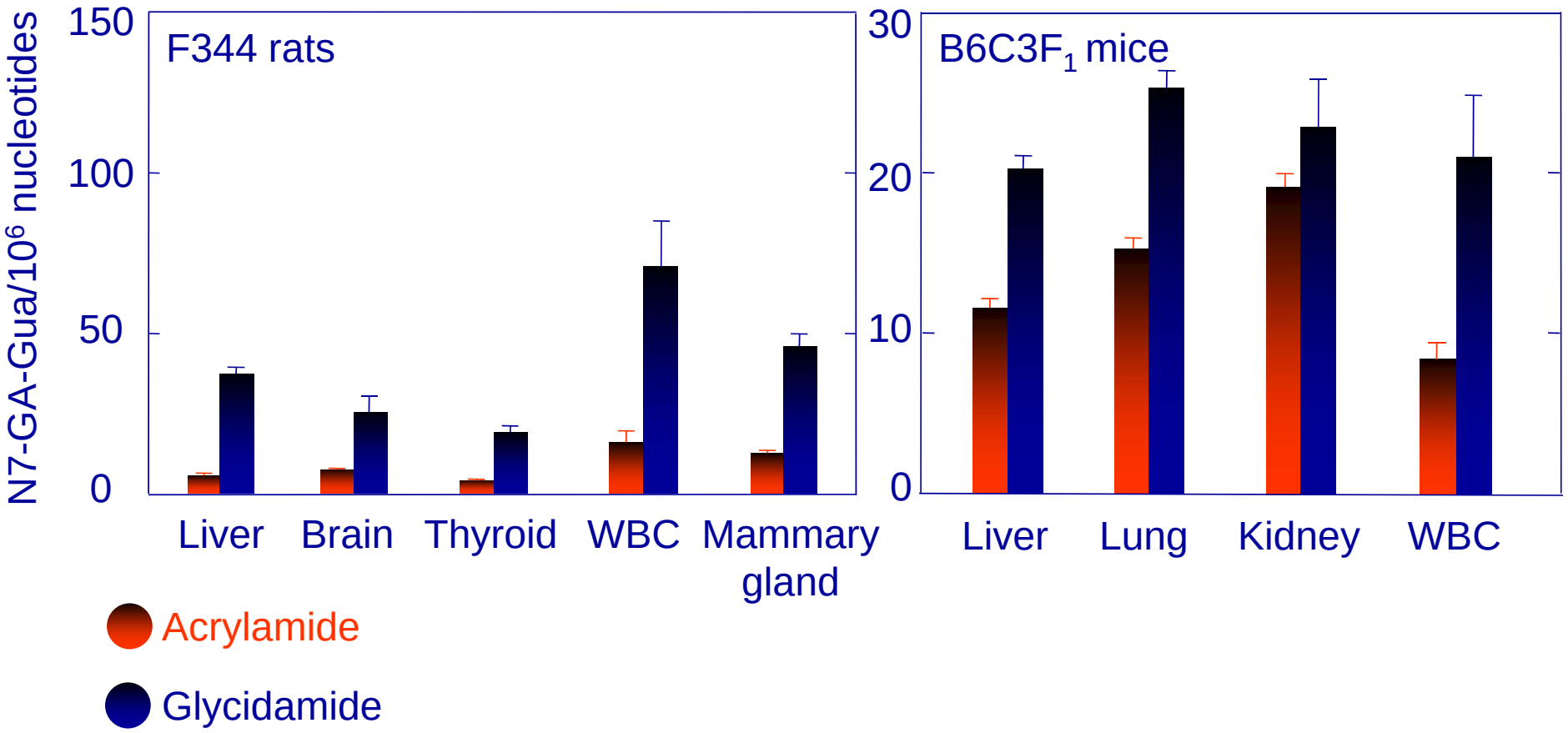


N7-(2-Carbamoyl-2-hydroxy-ethyl)guanine (N7-GA-Gua)



N3-(2-Carbamoyl-2-hydroxy-ethyl)adenine (N3-GA-dA) [Minor adduct]

N7-GA-GUA LEVELS IN F344 RATS AND B6C3F$_1$ MICE



HYPOTHESES

- Acrylamide is a genotoxic carcinogen as a result of metabolic conversion to glycidamide, which reacts with DNA
- Since the metabolic conversion of acrylamide to glycidamide occurs to a greater extent in mice as compared to rats, mice should be more sensitive than rats to the carcinogenic effects of acrylamide

GENERAL STUDY DESIGN

- Assess the carcinogenicity of acrylamide and its metabolite glycidamide in male and female B6C3F$_1$ mice and F344 rats treated chronically for two years.
- Acrylamide results formed the basis of NTP Technical Report 575.
- Glycidamide results form the basis of NTP Technical Report 588.

F344 RATS: OBSERVATIONS AND NON-NEOPLASTIC LESIONS IN 2-WEEK STUDIES

F344 rats	Acrylamide[a]		Glycidamide[a]	
	3.52 mM	7.03 mM	3.52 mM	7.03 mM
Males				
Hind-limb paresis	0/4	4/4	0/4	4/4
Urinary bladder dilatation	1/4	4/4	0/4	3/4
Testes seminiferous degeneration	0/4	4/4	0/4	4/4
Females				
Hind-limb paresis	0/4	4/4	0/4	1/4
Urinary bladder dilatation	0/4	4/4	0/4	1/4

[a]No adverse effects with 0.14, 0.35, 0.70, or 1.41 mM acrylamide or glycidamide.

F344 RATS: OBSERVATIONS AND NON-NEOPLASTIC LESIONS IN 3-MONTH STUDIES

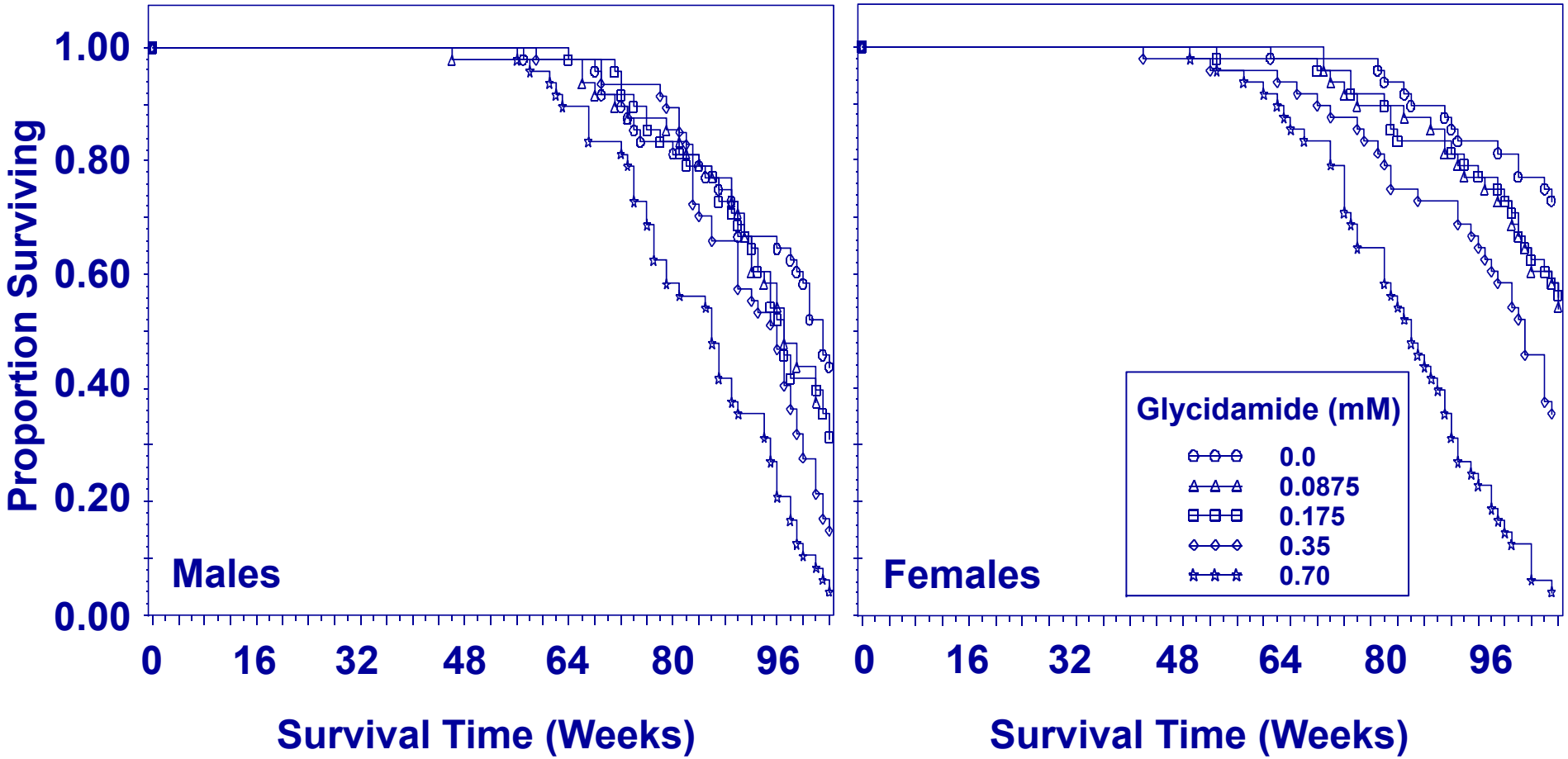
F344 rats	Acrylamide[a]		Glycidamide[a]	
	1.41 mM	3.52 mM	1.41 mM	3.52 mM
Males				
Hind-limb paresis	0/8	8/8	0/8	8/8
Axon degeneration	0/8	8/8	-[b]	0/8
Urinary bladder dilatation	0/8	8/8	-	2/8
Females				
Hind-limb paresis	4/8	8/8	0/8	8/8
Axon degeneration	0/8	8/8	-	1/8
Urinary bladder dilatation	4/8	8/8	-	0/8

[a]No adverse effects with 0.14, 0.35, or 0.70 mM acrylamide or glycidamide.
[b]Not examined.

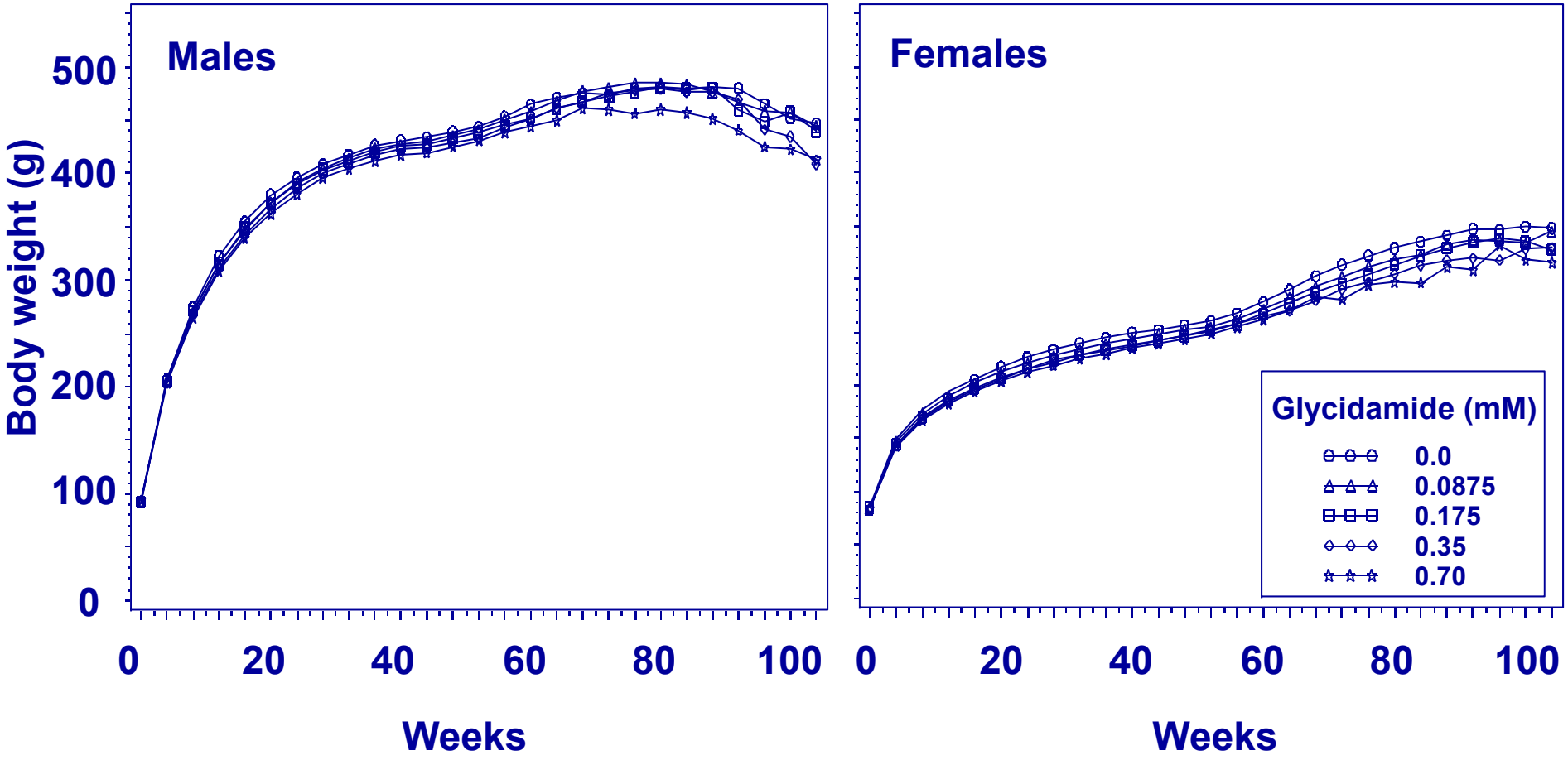
F344 RATS 2-YEAR GLYCIDAMIDE STUDY

- Male and female F344/N Nctr rats (48 rats/sex/group)
- Drinking water
- Doses:
  - 0, 0.0875, 0.175, 0.35, & 0.70 mM glycidamide
    (0 - ~4.0 mg glycidamide/kg bw/day)

SURVIVAL OF F344 RATS ADMINISTERED GLYCIDAMIDE



BODY WEIGHTS OF F344 RATS ADMINISTERED GLYCIDAMIDE



NEOPLASMS IN MALE F344 RATS ADMINISTERED GLYCIDAMIDE (Clear evidence)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Epididymis or testes, malignant mesothelioma[a]	0/48 (0%)†	1/48 (2%)	3/48 (6%)	10/47 (21%)*	17/48 (35%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	2/48 (4%)†	2/48 (4%)	1/48 (2%)	5/48 (10%)	8/48 (17%)*#

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

#Significantly different ($p< 0.05$) from the same dose level of glycidamide.

[a]NCTR historical control incidence range (all sites and all routes of exposure): 0.0 - 6.4%.

NEOPLASMS IN MALE F344 RATS ADMINISTERED GLYCIDAMIDE (Clear evidence)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Heart, malignant Schwannoma[a]	2/48 (4%)†	3/48 (6%)	3/48 (6%)	7/47 (15%)	8/48 (17%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	1/48 (2%)†	2/48 (4%)	3/48 (6%)	4/48 (8%)	6/48 (13%)*

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

[a]NCTR historical control incidence range (all routes of exposure): 0.0 - 2.1%.

NEOPLASMS IN MALE F344 RATS ADMINISTERED GLYCIDAMIDE (Clear evidence)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Thyroid gland, follicular cell adenoma or carcinoma[a]	2/47 (4%)†	3/42 (7%)	6/48 (13%)	4/47 (9%)	13/46 (28%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	1/47 (2%)†	3/48 (6%)	4/47 (9%)	6/48 (13%)	9/48 (19%)*

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

[a]NCTR historical control incidence range (all routes of exposure): 0.0 - 4.2%.

NEOPLASMS IN MALE F344 RATS ADMINISTERED GLYCIDAMIDE (Clear evidence)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Oral mucosa or tongue, squamous cell papilloma or carcinoma[a]	2/48 (4%)†	2/48 (4%)	2/48 (4%)	3/47 (6%)	7/48 (15%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	1/48 (2%)	1/48 (2%)	1/48 (2%)	5/48 (10%)	2/48 (4%)

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

[a]NCTR historical control incidence range (all routes of exposure): 0.0 - 2.1%.

NEOPLASMS IN MALE F344 RATS ADMINISTERED GLYCIDAMIDE (May have been related to treatment)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Mononuclear cell leukemia[a]	21/48 (44%)[†]	26/48 (54%)	27/48 (56%)	27/47 (57%)	31/48 (65%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	31/48 (65%)	22/48 (46%)	23/48 (48%)	32/48 (67%)	28/48 (58%)

[†]Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

[a]NCTR historical control incidence range (all routes of exposure): 31 - 65%.

NEOPLASMS IN FEMALE F344 RATS ADMINISTERED GLYCIDAMIDE (Clear evidence)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Mammary gland, fibroadenoma[a]	16/48 (33%)†	26/48 (54%)*	35/48 (73%)*	33/48 (69%)*	36/48 (75%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	16/48 (33%)†	18/48 (38%)	24/46 (52%)*	22/47 (47%)*#	31/48 (65%)*

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

#Significantly different ($p< 0.05$) from the same dose level of glycidamide.

[a]NCTR historical control incidence range (all routes of exposure): 26 - 43%.

NEOPLASMS IN FEMALE F344 RATS ADMINISTERED GLYCIDAMIDE (Clear evidence)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Thyroid gland, follicular cell adenoma or carcinoma[a]	0/48 (0%)†	3/48 (6%)	5/46 (11%)*	4/46 (9%)*	8/47 (17%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	0/48 (0%)†	0/48 (0%)	2/48 (4%)	3/48 (6%)	4/47 (9%)*

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

[a]NCTR historical control incidence range (all routes of exposure): 0.0 - 2.9%.

NEOPLASMS IN FEMALE F344 RATS ADMINISTERED GLYCIDAMIDE (Clear evidence)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Oral mucosa or tongue, squamous cell papilloma or carcinoma[a]	1/48 (2%)†	2/48 (4%)	2/48 (4%)	2/48 (4%)	7/48 (15%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	0/48 (0%)†	2/48 (4%)	1/48 (2%)	3/48 (6%)	5/48 (10%)*

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

[a]NCTR historical control incidence range (all routes of exposure): 0.0 - 2.1%.

NEOPLASMS IN FEMALE F344 RATS ADMINISTERED GLYCIDAMIDE (Clear evidence)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Clitoral gland, carcinoma	4/48 (8%)†	6/48 (13%)	7/48 (15%)	11/48 (23%)*	14/47 (30%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	1/48 (2%)†	6/48 (13%)*	12/47 (26%)*	3/48 (6%)#	8/47 (17%)*

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

#Significantly different ($p< 0.05$) from the same dose level of glycidamide.

[a]NCTR historical control incidence range (all routes of exposure): 0.0 - 10.4%.

NEOPLASMS IN FEMALE F344 RATS ADMINISTERED GLYCIDAMIDE (Were also related to treatment)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Forestomach, squamous cell papilloma[a]	0/48 (0%)†	1/48 (2%)	0/48 (0%)	0/47 (0%)	3/46 (7%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	0/48 (0%)	0/48 (0%)	2/48 (4%)	0/48 (0%)	0/48 (0%)

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

[a]NCTR historical control incidence range (all routes of exposure): 0.0 - 2.1%.

NEOPLASMS IN FEMALE F344 RATS ADMINISTERED GLYCIDAMIDE (Were also related to treatment)

Neoplasm	Glycidamide (mM)				
Mononuclear cell leukemia[a]	14/48 (29%)†	11/48 (23%)	21/48 (44%)	19/48 (40%)	27/48 (56%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	10/48 (21%)	19/48 (40%)	19/48 (40%)	15/48 (31%)	17/48 (35%)

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

[a]NCTR historical control incidence range (all routes of exposure): 13 - 45%.

NON-NEOPLASTIC LESIONS IN F344 RATS ADMINISTERED GLYCIDAMIDE

Sex	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Males					
Brain, gliosis	0/48†	1/48	0/48	0/47	4/48*
	-	1.0[a]	-	-	2.8
Females					
Brain, gliosis	0/48†	0/48	4/48	4/48*	4/48*
	-	-	2.5	2.0	2.5
Spinal cord (lumbar), axon degeneration	5/48†	6/48	5/47	6/48	9/48*
	1.0	1.0	1.0	1.0	1.0

[a]Average severity: 1, minimal; 2, mild; 3, moderate; 4 marked.

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

NON-NEOPLASTIC LESIONS IN F344 RATS ADMINISTERED GLYCIDAMIDE (CONTINUED)

- Male rats
  - Epididymis, exfoliated germ cells
  - Liver, hepatocyte degeneration
  - Liver, necrosis
- Female rats
  - Bone marrow, hyperplasia
  - Uterus, endometrial cystic hyperplasia

$B6C3F_1$ MICE: OBSERVATIONS IN 2-WEEK STUDIES

$B6C3F_1$ mice	Acrylamide[a]		Glycidamide[a]	
	3.52 mM	7.03 mM	3.52 mM	7.03 mM
Males				
Hind-limb paresis	0/4	1/4[b]	0/4	0/4
Females				
Hind-limb paresis	0/4	1/4[b]	0/4	0/4

[a]No adverse effects with 0.14, 0.35, 0.70, or 1.41 mM acrylamide or glycidamide.

[b]Mice did not survive the 2-week treatment period.

B6C3F$_1$ MICE: OBSERVATIONS AND NON-NEOPLASTIC LESIONS IN 3-MONTH STUDIES

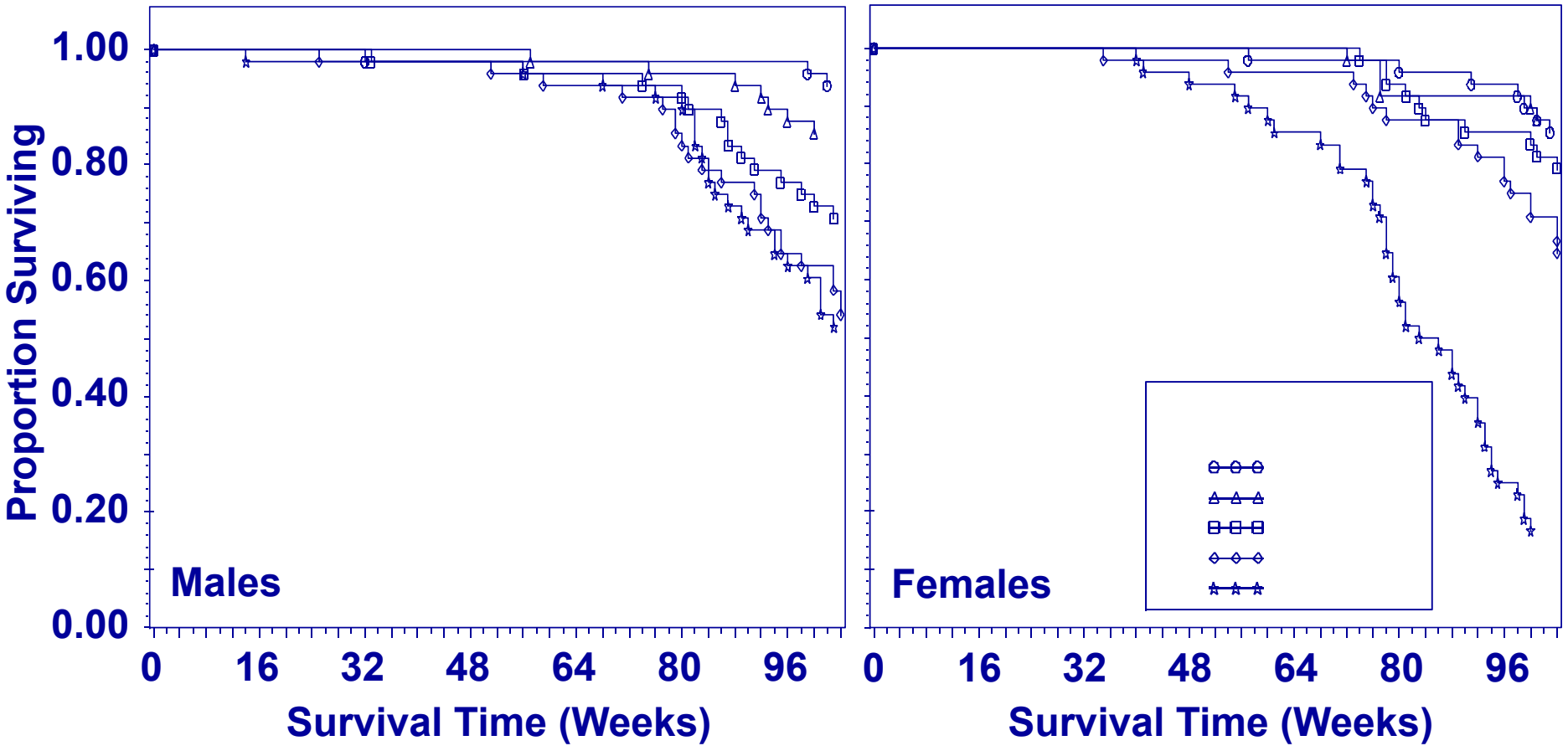
B6C3F$_1$ mice	Acrylamide[a]		Glycidamide[a]	
	1.41 mM	3.52 mM	1.41 mM	3.52 mM
Males				
Hind-limb paresis	0/8	8/8	0/8	2/8
Axon degeneration	0/8	8/8	-[b]	1/8
Urinary bladder dilatation	0/8	8/8	-	1/8
Females				
Hind-limb paresis	0/8	8/8	0/8	0/8
Axon degeneration	0/8	8/8	-	1/8
Urinary bladder dilatation	0/8	4/8	-	0/8

[a]No adverse effects with 0.14, 0.35, or 0.70 mM acrylamide or glycidamide.
[b]Not examined.

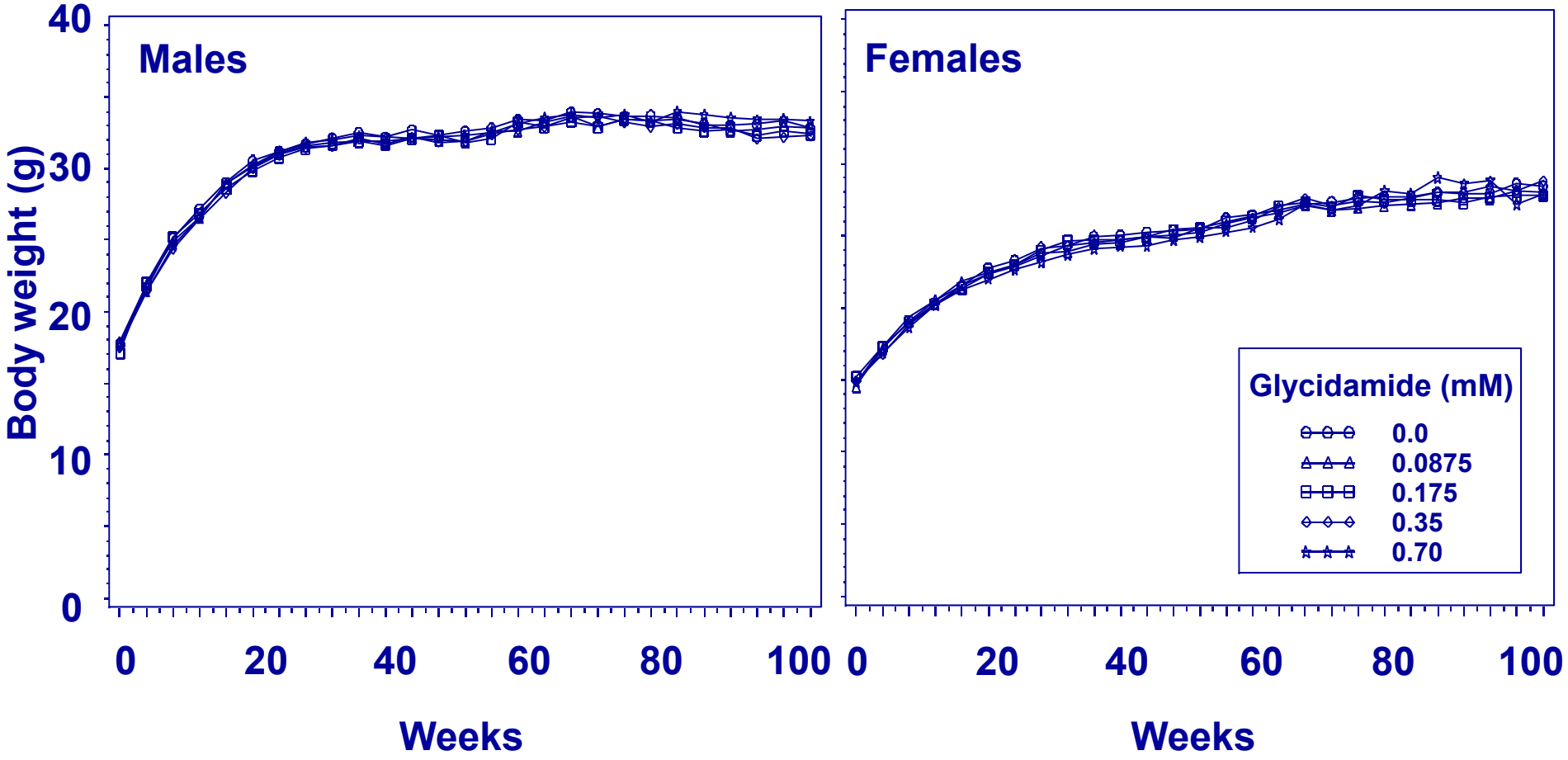
B6C3F$_1$ MICE 2-YEAR GLYCIDAMIDE STUDY

- Male and female B6C3F$_1$/Nctr mice (48 mice/sex/group)
- Drinking water
- Doses:
  - 0, 0.0875, 0.175, 0.35, & 0.70 mM glycidamide (0 - ~11.3 mg glycidamide/kg bw/day)

SURVIVAL OF B6C3F$_1$ MICE ADMINISTERED GLYCIDAMIDE



BODY WEIGHTS OF B6C3F$_1$ MICE ADMINISTERED GLYCIDAMIDE



NEOPLASMS IN MALE B6C3F$_1$ MICE ADMINISTERED GLYCIDAMIDE (Clear evidence)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Harderian gland, adenoma[a]	3/47 (6%)†	17/47 (36%)*	23/47 (49%)*	32/46 (70%)*	42/47 (89%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	2/46 (4%)†	13/46 (28%)*	27/47 (57%)*	36/47 (77%)*	39/47 (83%)*

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

[a]NCTR historical control incidence range (all routes of exposure): 0.0 - 10.6%.

NEOPLASMS IN MALE B6C3F$_1$ MICE ADMINISTERED GLYCIDAMIDE (Clear evidence)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Lung, alveolar/bronchiolar adenoma or carcinoma[a]	0/47 (0%)†	7/46 (15%)*	8/47 (17%)*	13/47 (28%)*	19/47 (40%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	6/47 (13%)†	6/46 (13%)	14/47 (30%)*	10/45 (22%)	20/48 (42%)*

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

[a]NCTR historical control incidence range (all routes of exposure): 10 - 31%.

NEOPLASMS IN MALE B6C3F$_1$ MICE ADMINISTERED GLYCIDAMIDE (Clear evidence)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Forestomach, squamous cell papilloma or carcinoma[a]	0/47 (0%)†	2/45 (4%)	3/48 (6%)	2/45 (4%)	12/41 (29%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	0/46 (0%)†	2/45 (4%)	2/46 (4%)	7/47 (15%)*	8/44 (18%)*

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

[a]NCTR historical control incidence range (all routes of exposure): 0.0 - 2.1%.

NEOPLASMS IN MALE B6C3F$_1$ MICE ADMINISTERED GLYCIDAMIDE (Clear evidence)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Skin, squamous cell papilloma or carcinoma[a]	0/47 (0%)†	1/48 (2%)	2/47 (4%)	1/47 (2%)	9/46 (20%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	1/47 (2%)†	0/47 (0%)	0/47 (0%)	2/47 (4%)	3/46 (7%)

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

[a]NCTR historical control incidence range (all routes of exposure): 0.0 - 2.1%.

NEOPLASMS IN FEMALE B6C3F$_1$ MICE ADMINISTERED GLYCIDAMIDE (Clear evidence)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Harderian gland, adenoma[a]	2/45 (4%)†	19/47 (40%)*	20/47 (43%)*	24/46 (52%)*	40/46 (87%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	0/45 (0%)†	8/44 (18%)*#	20/48 (42%)*	32/47 (68%)*	31/43 (72%)*

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

#Significantly different ($p< 0.05$) from the same dose level of glycidamide.

[a]NCTR historical control incidence range (all routes of exposure): 0.0 - 8.7%.

NEOPLASMS IN FEMALE B6C3F$_1$ MICE ADMINISTERED GLYCIDAMIDE (Clear evidence)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Lung, alveolar/bronchiolar adenoma or carcinoma[a]	4/46 (9%)†	6/48 (13%)	3/47 (6%)	8/47 (17%)	11/44 (25%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	2/47 (4%)†	4/47 (9%)	6/48 (13%)	11/45 (24%)*	20/45 (44%)*

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

[a]NCTR historical control incidence range (all routes of exposure): 2.1 - 12.5%.

NEOPLASMS IN FEMALE B6C3F$_1$ MICE ADMINISTERED GLYCIDAMIDE (Clear evidence)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Mammary gland, adenoacanthoma or adenocarcinoma[a]	1/45 (2%)†	1/48 (2%)	2/47 (4%)	9/47 (19%)*	18/45 (40%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	0/47 (0%)†	4/46 (9%)	7/48 (15%)*	4/45 (9%)*	17/42 (41%)*

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

[a]NCTR historical control incidence range (all routes of exposure): 0.0 - 11.4%.

NEOPLASMS IN FEMALE B6C3F$_1$ MICE ADMINISTERED GLYCIDAMIDE (Clear evidence)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Forestomach, squamous cell papilloma[a]	1/45 (2%)†	1/45 (2%)	1/47 (2%)	5/45 (11%)	9/44 (21%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	4/46 (9%)†	0/46 (0%)	2/48 (4%)	5/45 (11%)	8/42 (19%)

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

[a]NCTR historical control incidence range (all routes of exposure): 0.0 - 8.7%.

NEOPLASMS IN FEMALE B6C3F$_1$ MICE ADMINISTERED GLYCIDAMIDE (Clear evidence)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Skin, malignant mesenchymal neoplasms	0/45 (0%)†	1/48 (2%)	3/47 (6%)	5/47 (11%)*	12/45 (27%)*
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	0/48 (0%)†	0/46 (0%)	3/48 (6%)	10/45 (22%)*	6/43 (14%)*

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

[a]NCTR historical control incidence range (all routes of exposure): 0.0 - 11.4%.

NEOPLASMS IN FEMALE B6C3F$_1$ MICE ADMINISTERED GLYCIDAMIDE (May have been related to treatment)

Neoplasm	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Ovary, benign granulosa cell tumor	0/45 (0%)†	0/47 (0%)	0/47 (0%)	1/46 (2%)	2/44 (5%)
	Acrylamide (mM)				
	0	0.0875	0.175	0.35	0.70
	0/46 (0%)†	1/45 (2%)	0/48 (0%)	1/45 (2%)	5/42 (12%)*

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

[a]NCTR historical control incidence range (all routes of exposure): 0.0 – 0.7%.

NON-NEOPLASTIC LESIONS IN MALE B6C3F$_1$ MICE ADMINISTERED GLYCIDAMIDE

Lesion	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Eye, cataract	1/47†	3/45	7/46*	8/44*	17/42*
	4.0[a]	1.0	2.1	2.3	2.0
Eye, corneal inflammation	0/47†	0/45	2/46	0/44	8/42*
	-	-	2.5	-	2.1

[a]Average severity: 1, minimal; 2, mild; 3, moderate; 4 marked.

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

NON-NEOPLASTIC LESIONS IN FEMALE $B6C3F_1$ MICE ADMINISTERED GLYCIDAMIDE

Lesion	Glycidamide (mM)				
	0	0.0875	0.175	0.35	0.70
Eye, cataract	1/45†	2/44	8/47*	8/44*	9/43*
	1.0[a]	3.0	3.1	2.5	1.6
Eye, corneal inflammation	0/45†	2/44	1/47	3/44	5/43*
	-	2.0	1.0	1.3	2.2
Liver, angiectasis	0/47†	0/48	1/47	0/46	5/43*
	-	-	2.0[a]	-	2.4
Liver, necrosis	0/47†	0/48	0/47	0/46	5/43*
	-	-	-	-	2.2

[a]Average severity: 1, minimal; 2, mild; 3, moderate; 4 marked.

†Significant ($p<0.05$) dose-related trend.

*Significantly different ($p<0.05$) from control.

NON-NEOPLASTIC LESIONS IN B6C3F$_1$ MICE ADMINISTERED GLYCIDAMIDE (CONTINUED)

- Male mice
  - Preputial gland, degeneration
  - Preputial gland, ductal dilatation
  - Preputial gland, inflammation
  - Spleen, hematopoietic cell proliferation
- Female mice
  - Spinal cord (cervical), axonal degeneration
  - Spleen, hematopoietic cell proliferation

COMPARISON OF TUMOR RESPONSE IN $B6C3F_1$ MICE AND F344 RATS ADMINISTERED ACRYLAMIDE

Species	Neoplasm	Sex	Acrylamide (BMD_{10}, µmol/kg bw/day)
$B6C3F_1$ mice	Harderian gland adenoma	Male	5.1-5.4
	Harderian gland adenoma	Female	6.7-7.3
F344 rats	Thyroid gland adenoma or carcinoma	Male	16.5-28.2
	Mammary gland fibroadenoma	Female	7.7-12.9

CONCLUSIONS: MALE F344 RATS

- *Clear evidence of carcinogenic activity* based on increased incidences of:
  - Malignant mesothelioma of the epididymis and testis
  - Malignant Schwannoma of the heart
  - Follicular cell adenoma or carcinoma of the thyroid gland
  - Oral cavity (oral mucosa or tongue) neoplasms (primarily papilloma)
- *May also have been related to treatment*:
  - Mononuclear cell leukemia

CONCLUSIONS: FEMALE F344 RATS

- ***Clear evidence of carcinogenic activity*** **based on increased incidences of:**
  - **Fibroadenoma of the mammary gland**
  - **Oral cavity (oral mucosa or tongue) neoplasms (primarily papilloma)**
  - **Follicular cell adenoma or carcinoma of the thyroid gland**
  - **Clitoral gland carcinoma**
- ***Were also related to treatment*****:**
  - **Forestomach squamous cell papilloma**
  - **Mononuclear cell leukemia**

CONCLUSIONS: MALE B6C3F$_1$ MICE

- *Clear evidence of carcinogenic activity* based on increased incidences of:
  - Harderian gland adenoma
  - Alveolar/bronchiolar neoplasms (primarily adenoma) of the lung
  - Squamous cell neoplasms (primarily papilloma) of the skin
  - Squamous cell neoplasms (primarily papilloma) of the forestomach

CONCLUSIONS: FEMALE B6C3F$_1$ MICE

- *Clear evidence of carcinogenic activity* based on increased incidences of:
  - Harderian gland adenoma
  - Alveolar/bronchiolar neoplasms (primarily adenoma) of the lung
  - Mammary gland adenoacanthoma and adenocarcinoma
  - Forestomach squamous cell papilloma
  - Malignant mesenchymal neoplasms of the skin
- *May have been related to treatment:*
  - Benign granulosa cell tumor of the ovary

SUMMARY

Acrylamide

Glycidamide

DNA

DNA adducts

The concordance of tumor sites between the acrylamide and glycidamide bioassays, coupled with the DNA adduct data, indicate that carcinogenic activity of acrylamide is due to its metabolic conversion to glycidamide.