



Memorandum

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Date July 24, 2007

From Mary E. Shackelford, PhD
Division of Food Contact Notifications, Toxicology Group 2

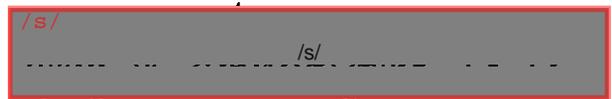
Subject Table of NOAELS and LOAELS from Bisphenol A Toxicity Studies in FMF 580

To Food Additive Master File 580

Through Michelle Twaroski, PhD
Team Leader, Toxicology Group 1, DFCN

A table of NOAELS and LOAELS has been constructed from the Bisphenol A toxicity studies which are located in Food Additive Master File 580. The information has been obtained from the following studies:

1. Teratologic Evaluation of Bisphenol A administered to CD-1 rats on gestation days 6-15 (NTP 85-089)
2. Teratologic Evaluation of Bisphenol A administered to CD-1 mice on gestation days 6-15 (NTP 85-088)
3. Bisphenol A: A reproduction and fertility assessment in CD-1 mice when administered in the feed (NTP 85-192)
4. Bisphenol A: A reproduction and fertility assessment in CD-1 mice when administered via subcutaneous silastic implants (NTP 84-105)



Mary E. Shackelford, PhD



Attachments: Tables of NOAELS and LOAELS from Bisphenol A toxicity studies

Study Type and Number	Study Design	Dose Levels	Endpoints Affected	NOEL
Teratology study in rats NTP-85-089	Gavage days 6 – 15 of gestation in CD ® rats	0, 160, 320, 640, or 1280 mg/kg/day Note: The 1280 mg/kg group was excluded due to issues with the replicates.	1. 25 % mortality in high dose group 2. Significant dose related decreases in maternal body weight gains at all dose levels	Maternal LOAEL 160 mg/kg/day Maternal NOAEL Not established Developmental LOAEL Not established Developmental NOAEL 1280 mg/kg/day
Teratology study in mice NTP-85-088	Gavage days 6-15 of gestation in CD-1 mice	0, 500, 750, 1000, or 1250 mg/kg/day	1. Mortality from low to high dose groups: 7.1%, 3.6%, 6.3%, 18.2% 2. Significant decrease in maternal body weight gains at the high dose 3. Significant increase in maternal relative liver weights in all dose groups 4. Significant increase in percent resorptions and non live implants per litter at the high dose group 5. Significant decrease in fetal body weights at the high dose group	Maternal LOAEL 500 mg/kg/day Maternal NOAEL Not established Developmental LOAEL 1250 mg/kg/day Developmental NOAEL 1000 mg/kg/day

Study Type and Number	Study Design	Dose Levels	Endpoints Affected	NOEL
<p>Reproduction and Fertility Assessment in CD-1 mice (diet)</p>	<p>Dietary feed, NTP's fertility assessment by continuous breeding Tasks 1-4</p> <p>Task 1 range-finding</p> <p>Task 2 continuous breeding for 98 days</p> <p>Task 3 crossover mating from 1% F0 animals and F0 controls in Task 2</p> <p>Task 4 F1 mating from last litter of Task 2</p>	<p>Task 1 - 0, 0.31, 0.62, 1.25, 2.5 and 5%</p> <p>Task 2 - 0, 0.25, 0.5, or 1%</p> <p>Task 3 - 0, 1%</p> <p>Task 4 - 0, 0.25, 0.5, or 1%</p>	<p><u>Task 2 0.5 & 1%</u></p> <p>1. significant reduction in mean number of live pups per litter</p> <p><u>Task 3 1% dose</u></p> <p>1. significant reduction in mean number of live pups per litter</p> <p>2. Significant increase in mean adjusted liver, adrenal, kidneys wts in males and females</p> <p>3 Hepatic and hepatic lesions males & females</p> <p>4. Significant decrease in adjusted seminal vesicle weight in males</p> <p>5. Significant decreases in sperm motility</p>	<p><u>Task 2</u></p> <p>F0 Reproductive LOAEL 0.5% diet</p> <p>F0 Reproductive NOAEL 0.25% diet</p> <p>F0 Systemic LOAEL and NOAEL Not determined as Only 1% dose level F0 Animals examined in Task 3</p> <p><u>Task 3</u></p> <p>No NOAELs or LOAELs were determined as only the high dose F0 animals were examined</p>

Study Type and Number	Study Design	Dose Levels	Endpoints Affected	NOEL
Reproduction and Fertility Assessment in CD-1 mice (diet) continued			<p><u>Task 4 F1 Males</u></p> <ol style="list-style-type: none"> 1. adjusted liver and kidney wts. increased significantly all doses 2. liver/kidney lesions in all groups 3. significant decreases in reproductive organ weight at all dose levels 4. decreased sperm motility at 0.5% <p><u>Task 4 F1 Females</u></p> <ol style="list-style-type: none"> 1. Significant increase in adjusted liver, kidney, adrenal wts in all doses 2. Liver/kidney lesions in all groups 	<p><u>Task 4</u></p> <p>F1 Reproductive LOAEL 0.25% diet</p> <p>F1 Reproductive NOAEL not determined</p> <p>F1 Systemic LOAEL 0.25%</p> <p>F1 Systemic NOAEL Not determined</p> <p><u>Overall conclusions</u> The LOAEL in the study was 0.25% for systemic and reproductive toxicity. No NOAEL for these parameters was determined.</p>

Study Type and Number	Study Design	Dose Levels	Endpoints Affected	NOEL
<p>Bisphenol A: Reproduction and Fertility Assessment in CD-1 Mice When Administered via Subcutaneous Silastic Implants</p>	<p>Silastic implants NTP's fertility assessment by continuous breeding Task 1 and 2 Task 1 Range-finding Task 2 continuous breeding for 98 days</p>	<p>Task 2 0 mg/implant, 25 mg/implant, 50 mg/implant, 100 mg/implant</p>	<p>Based on amount of bisphenol A in the implants at the beginning and end of the study the doses were: 11-12 3 mg (25 mg) 17.7-19.3 mg (50 mg) 37.2-40 mg (100 mg) No effects were observed on : Mean body weights Fertility Mean numbers litters Mean pup weights Organ weights (Control and high dose levels)</p>	<p>Authors concluded that implants were not appropriate for long term delivery because some implants were expelled and some were were locally toxic. Authors did not established LOAEL or NOAEL for the study.</p>