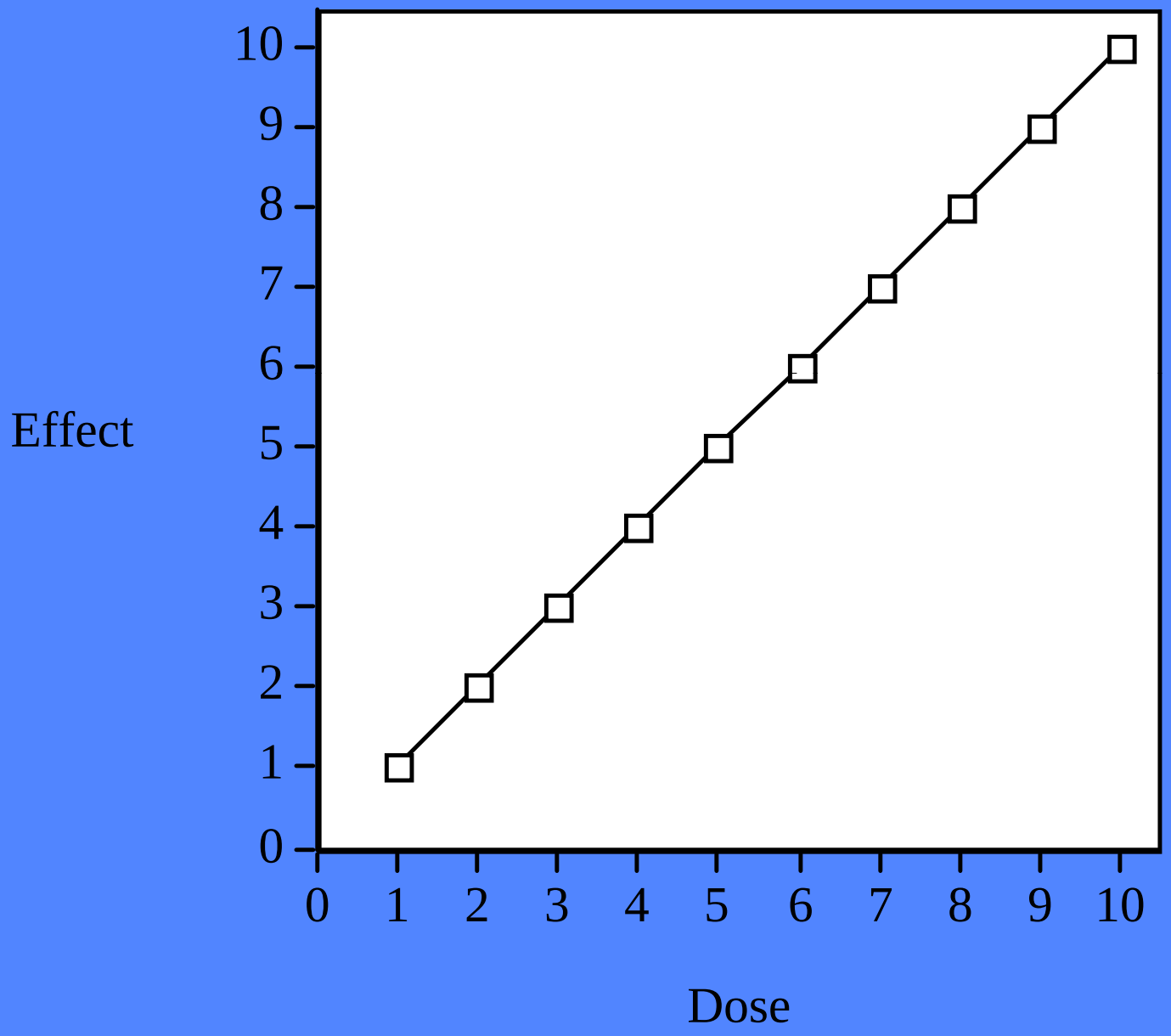
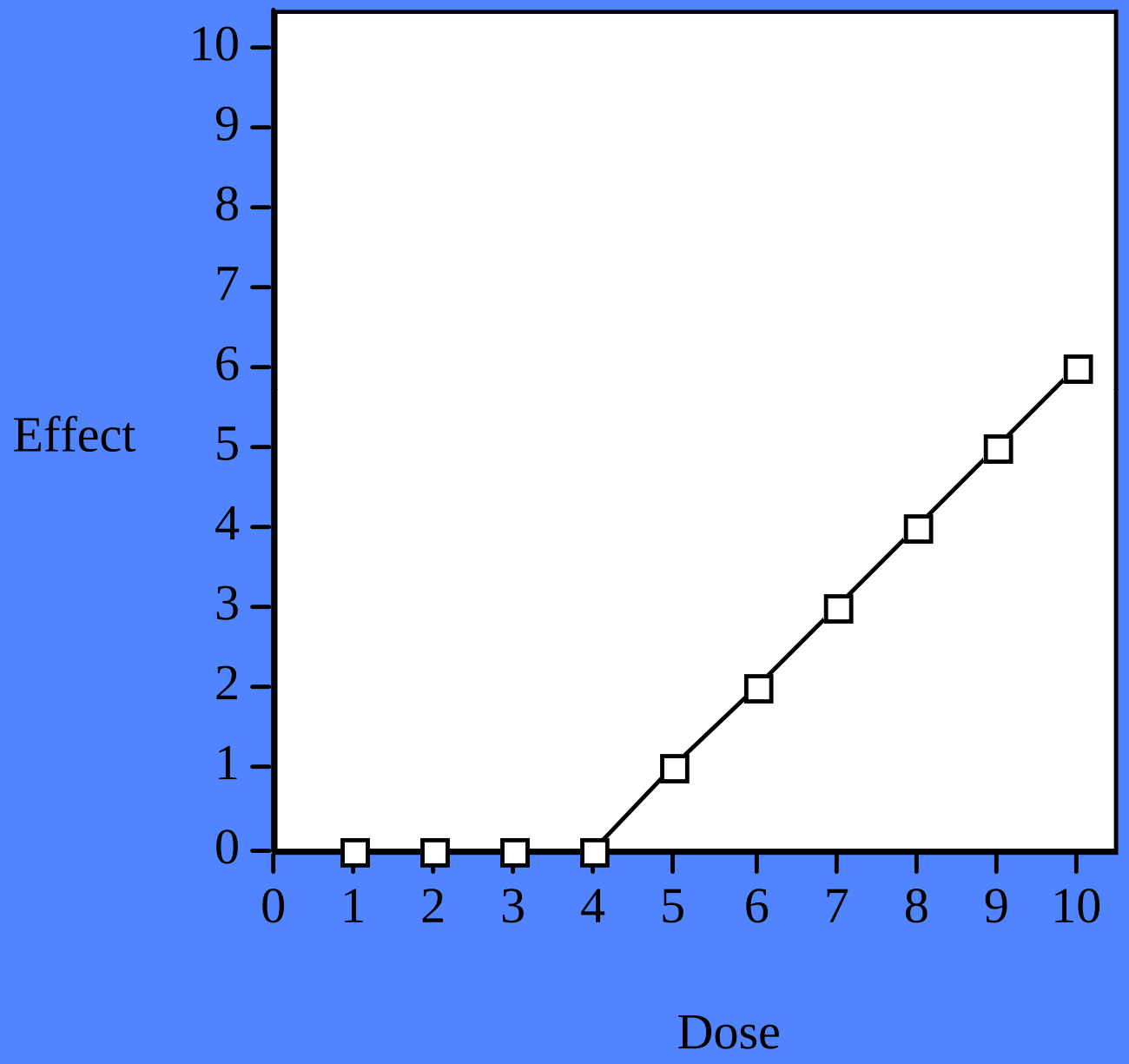
Non-Monotonic Dose-Toxicity Effects and Behavioral Function: Low-Dose Impairments from Developmental Pesticide Exposure

Edward D. Levin, Ph.D.
Department of Psychiatry and Behavioral Sciences
Duke University Medical Center

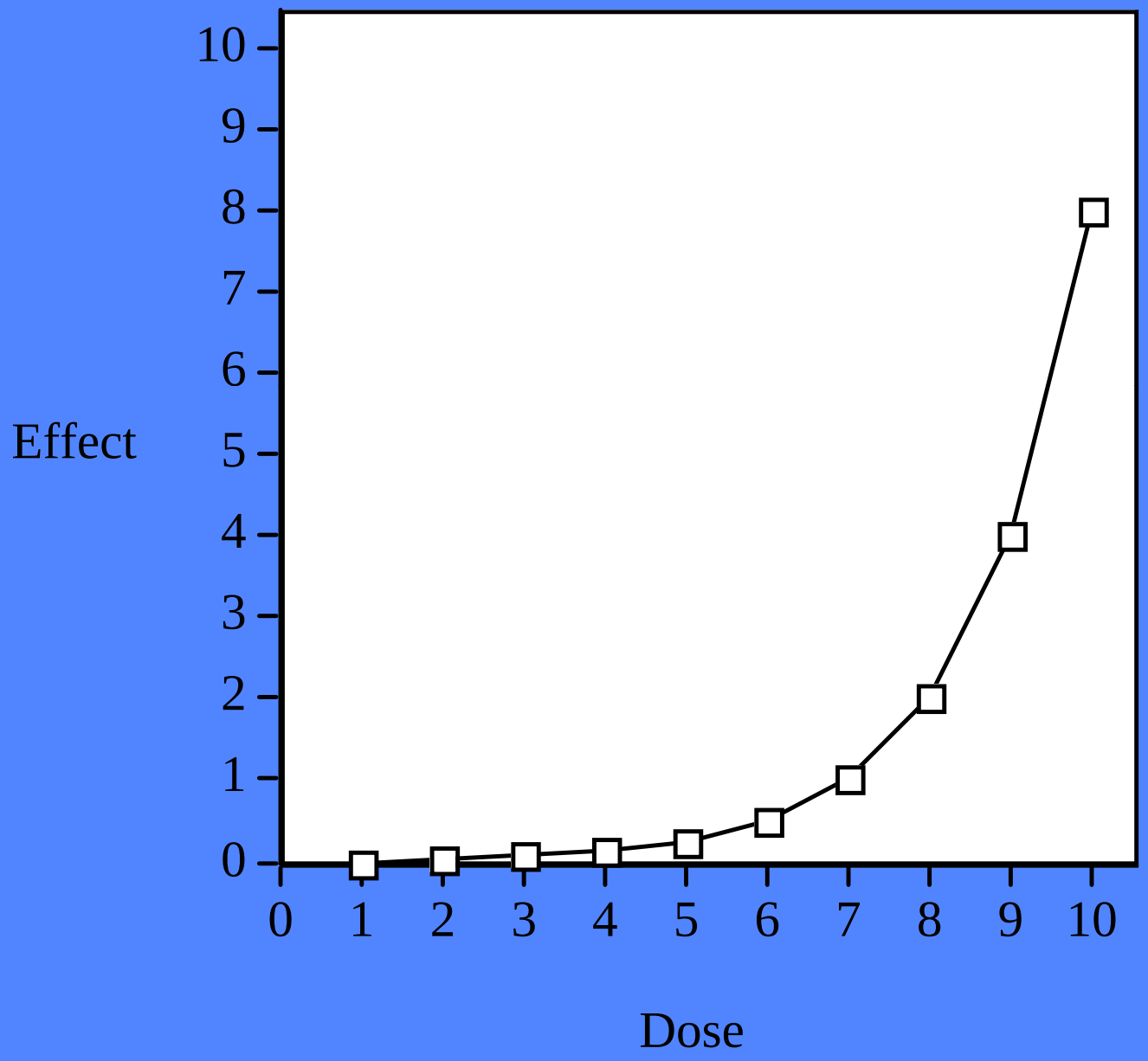
Linear Dose-Effect Function



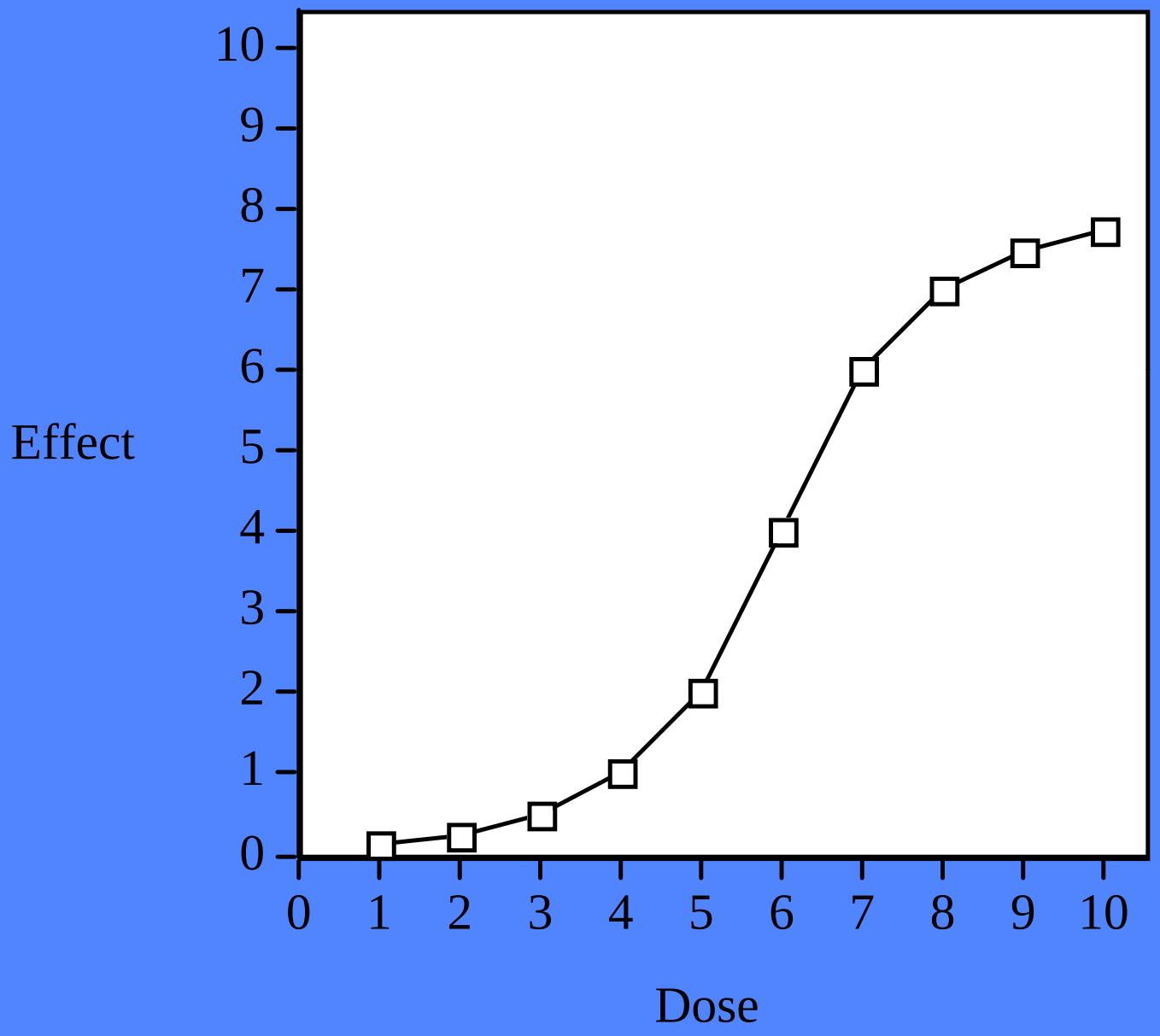
Linear Dose-Effect Function with Threshold



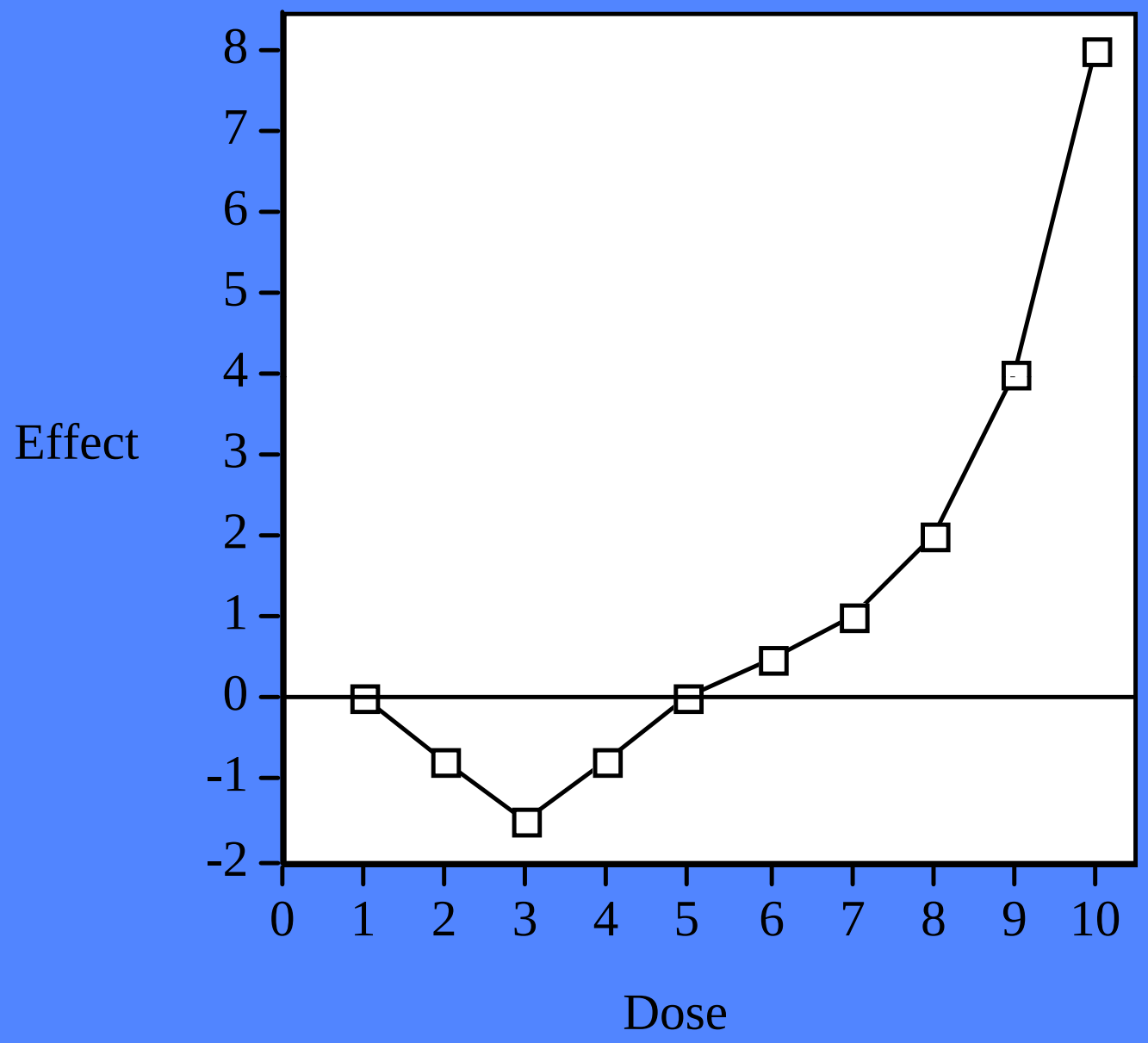
Non-Linear Dose-Effect Function



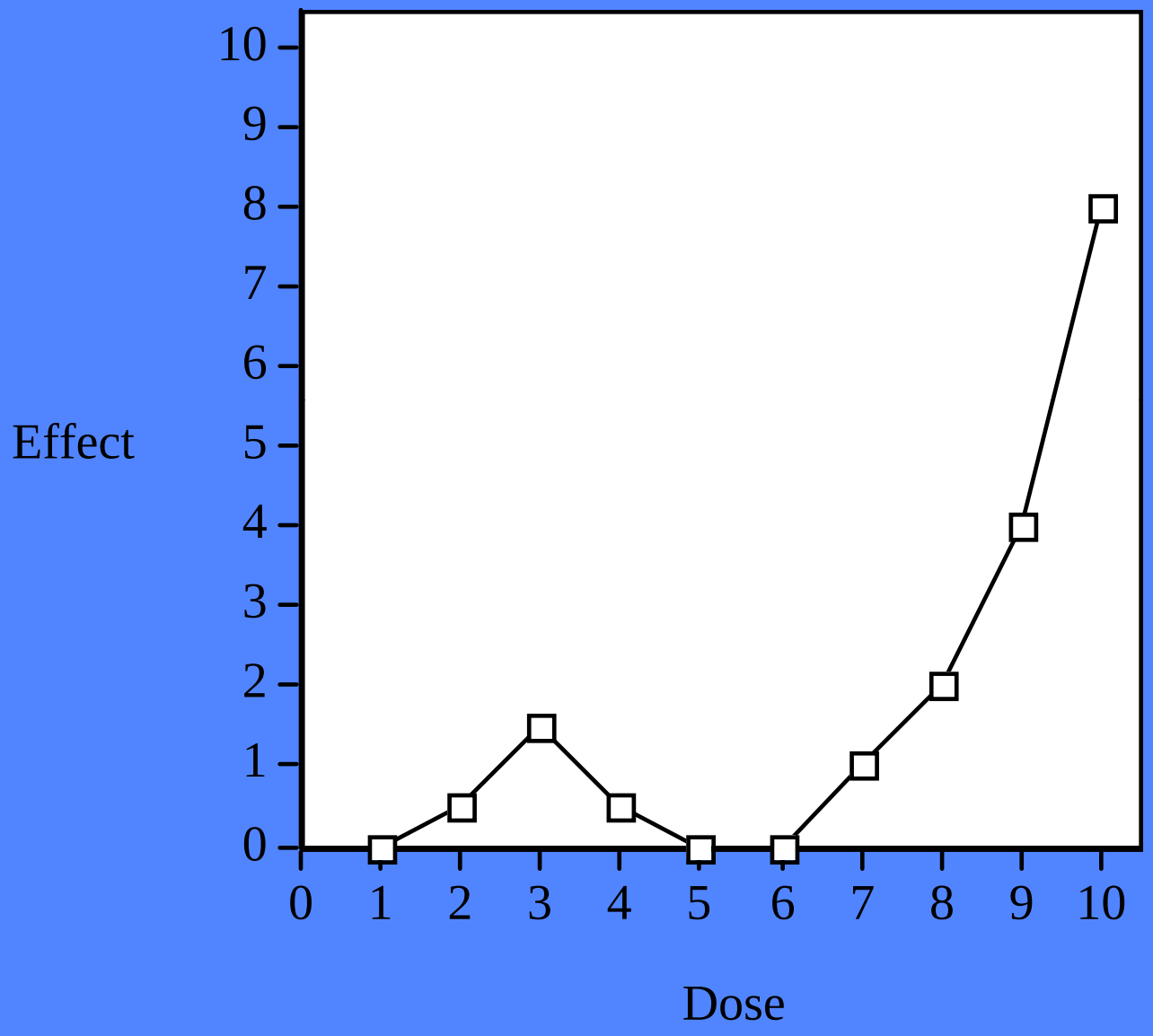
Non-Linear Dose-Effect Function: Sigmoid



Non-Monotonic Dose-Effect Function: Hormesis

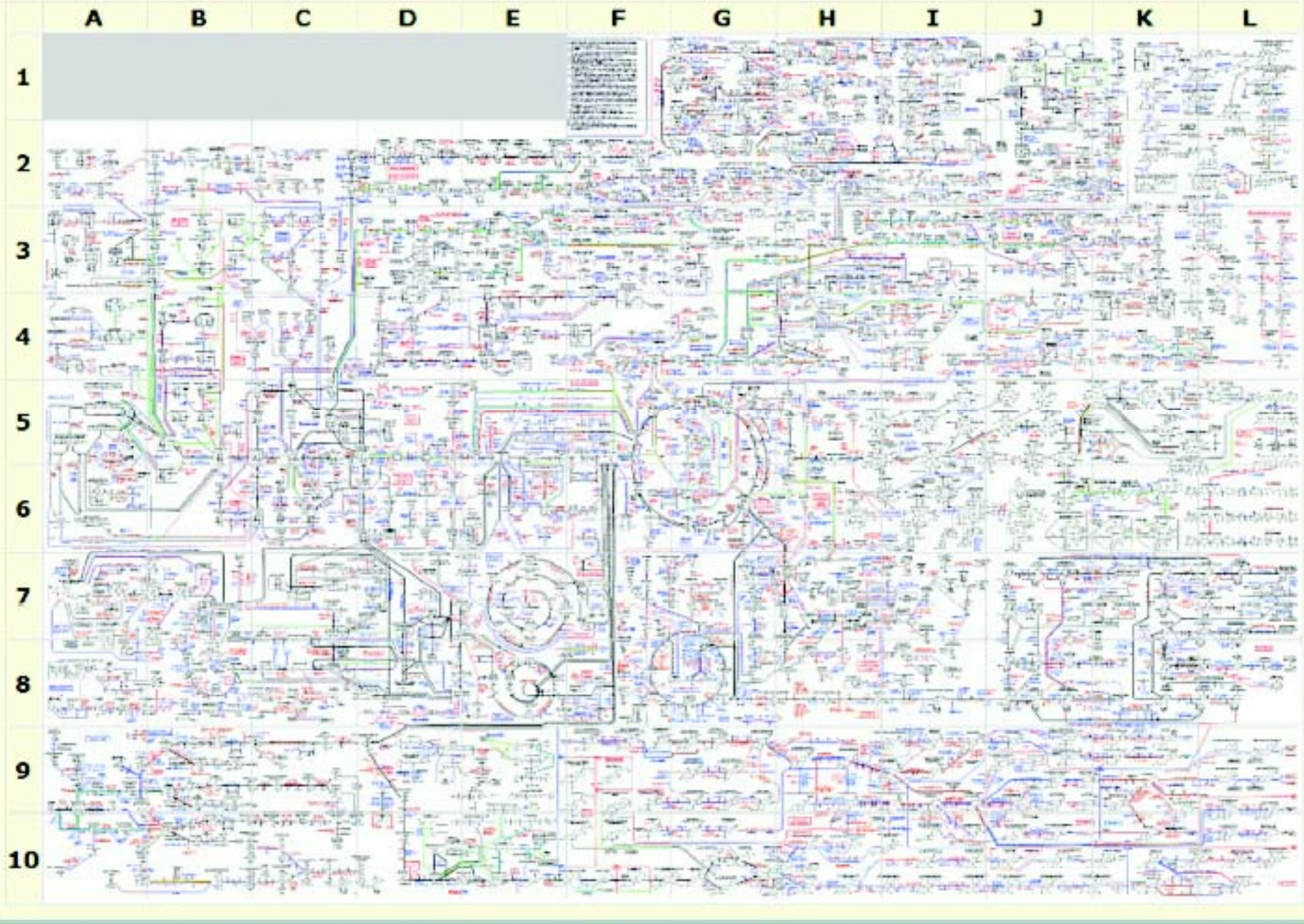


Non-Monotonic Dose-Effect Function: Low Dose Effect



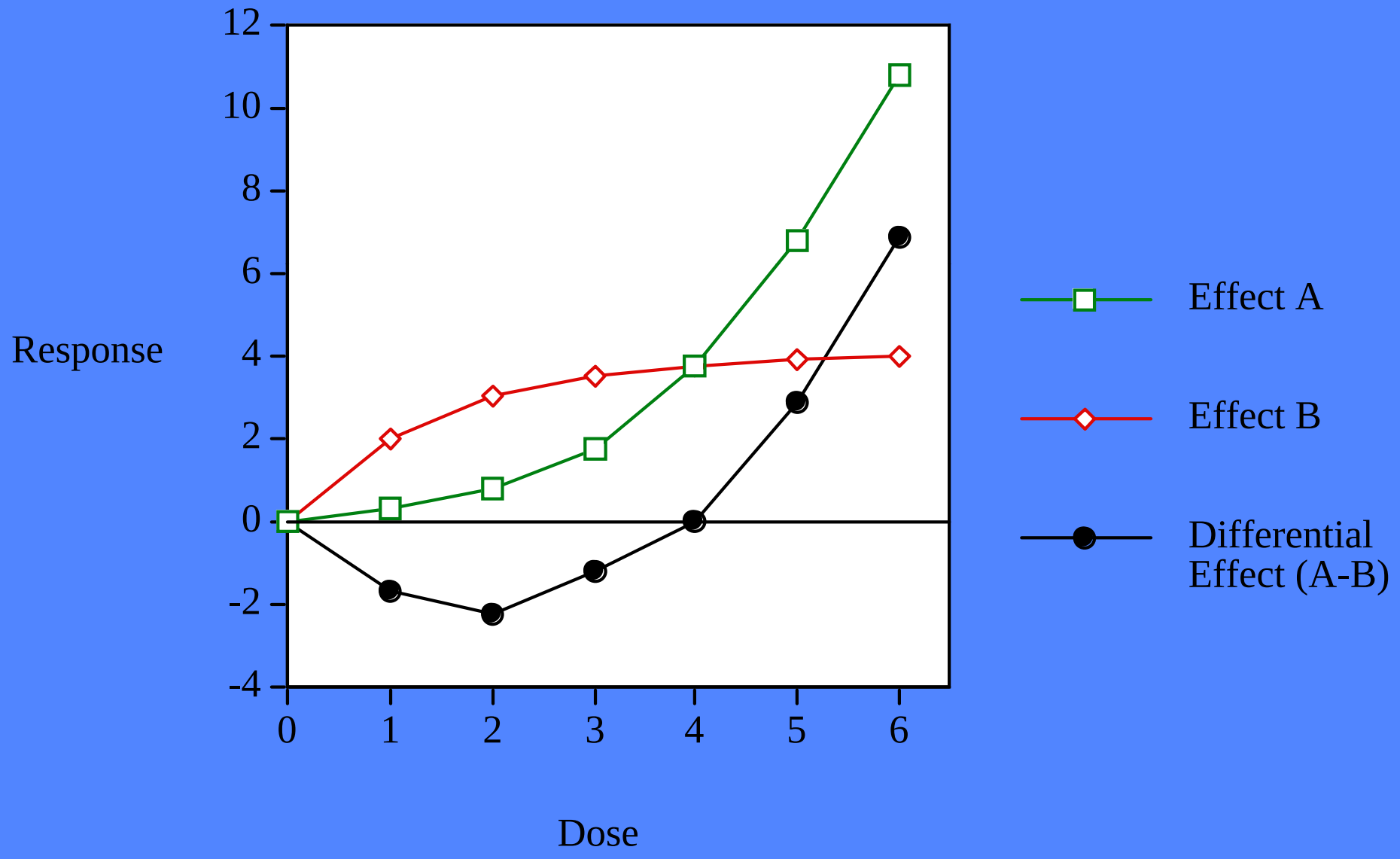
Toxicology is a Life Science

Life is Complex

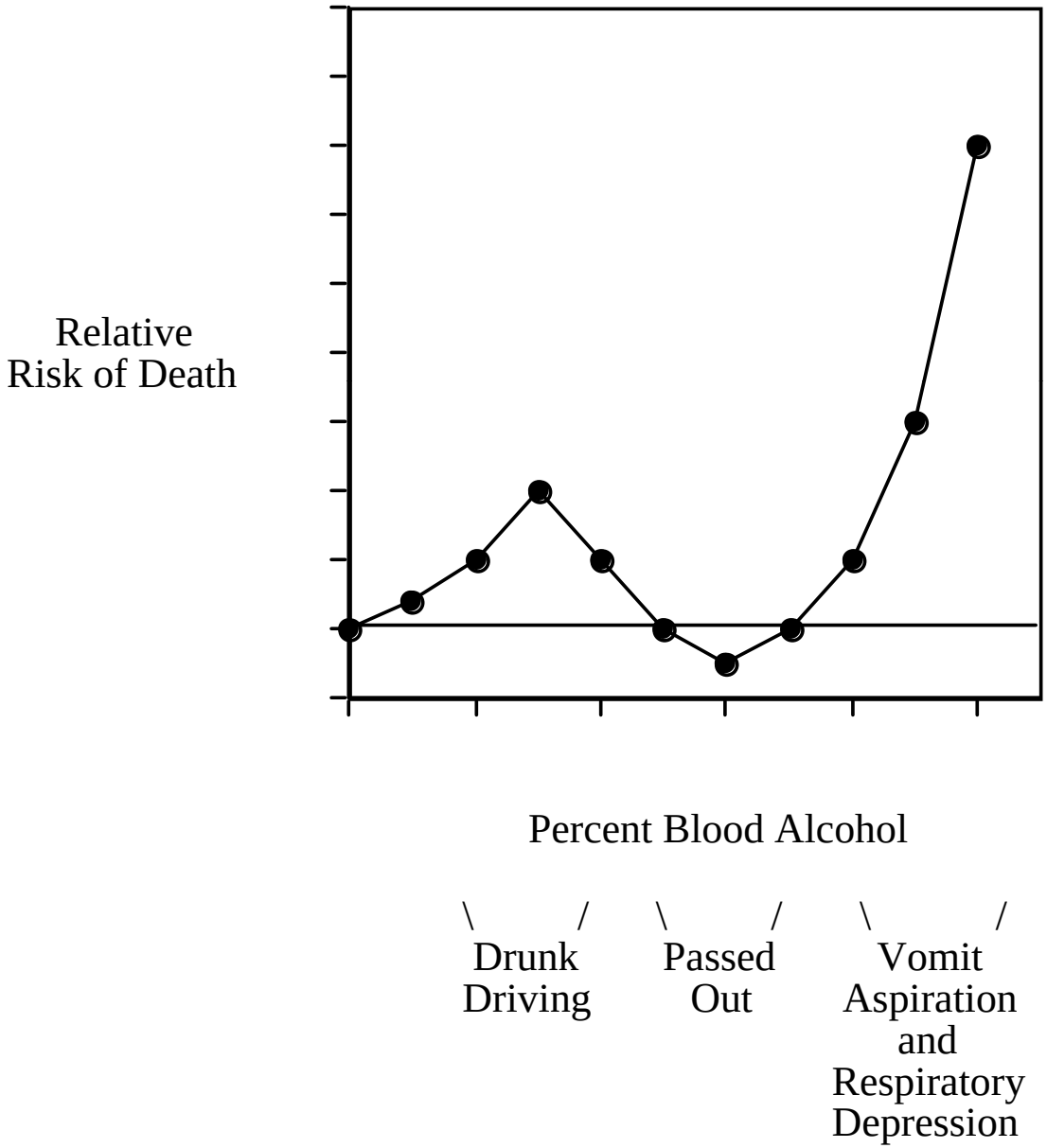


http://biochem.boehringer-mannheim.com/prodinfo_fst.htm?/techserv/metmap.htm

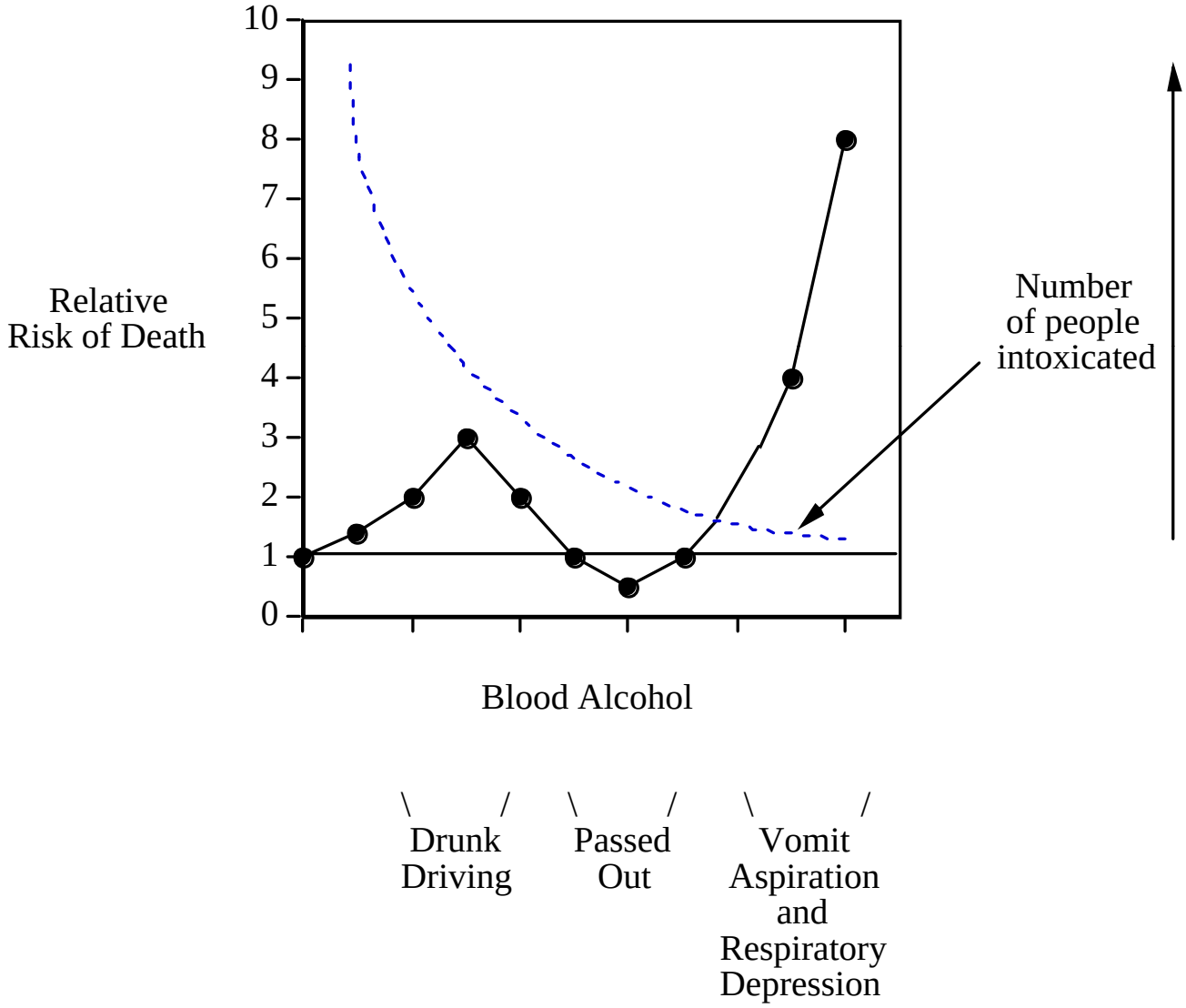
The Diffference of Two Monotonic Effects Can Result in a Non-Monotonic Function



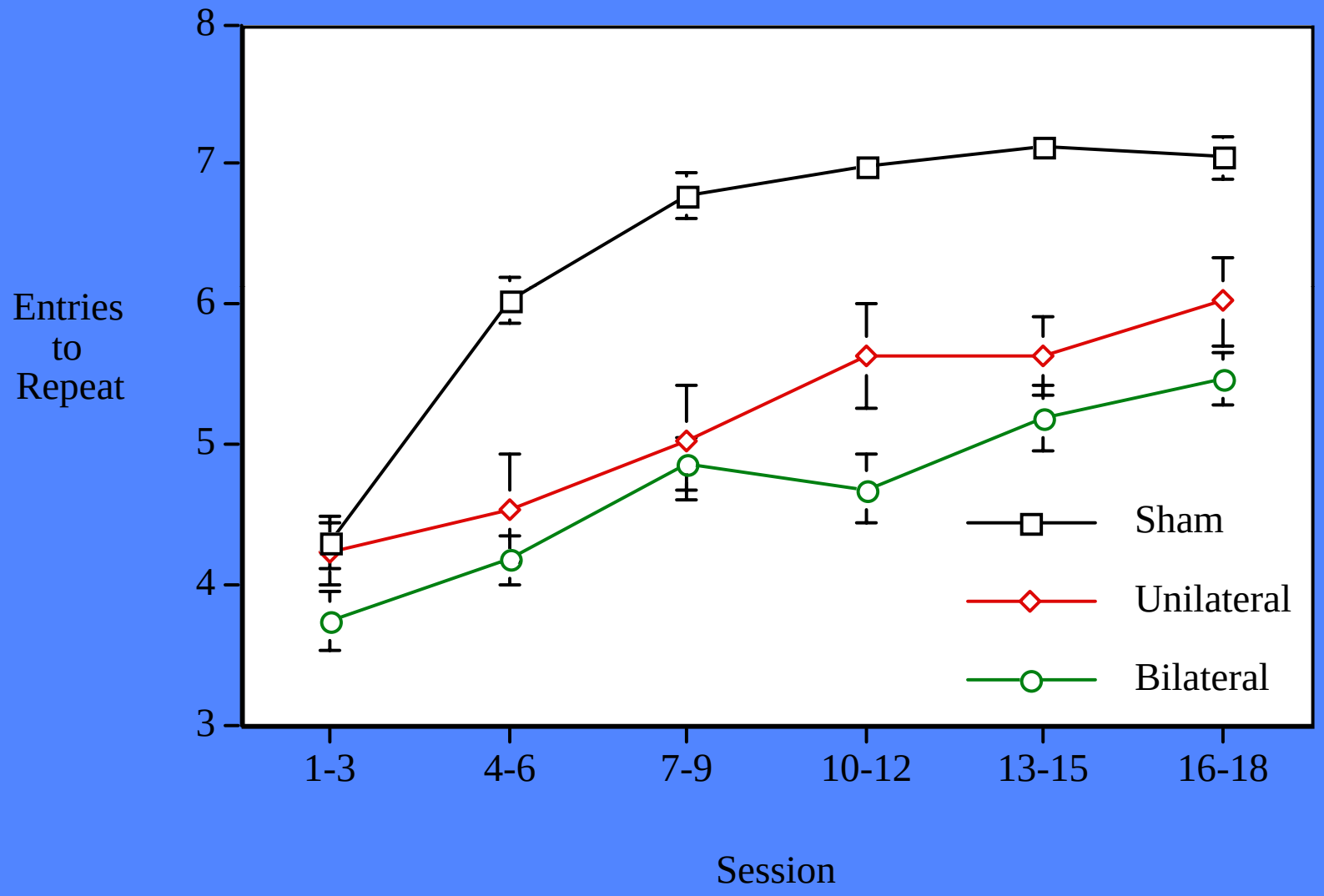
Theoretical Triphasic Dose-Effect Function of Lethal Risk from Alcohol Intoxication



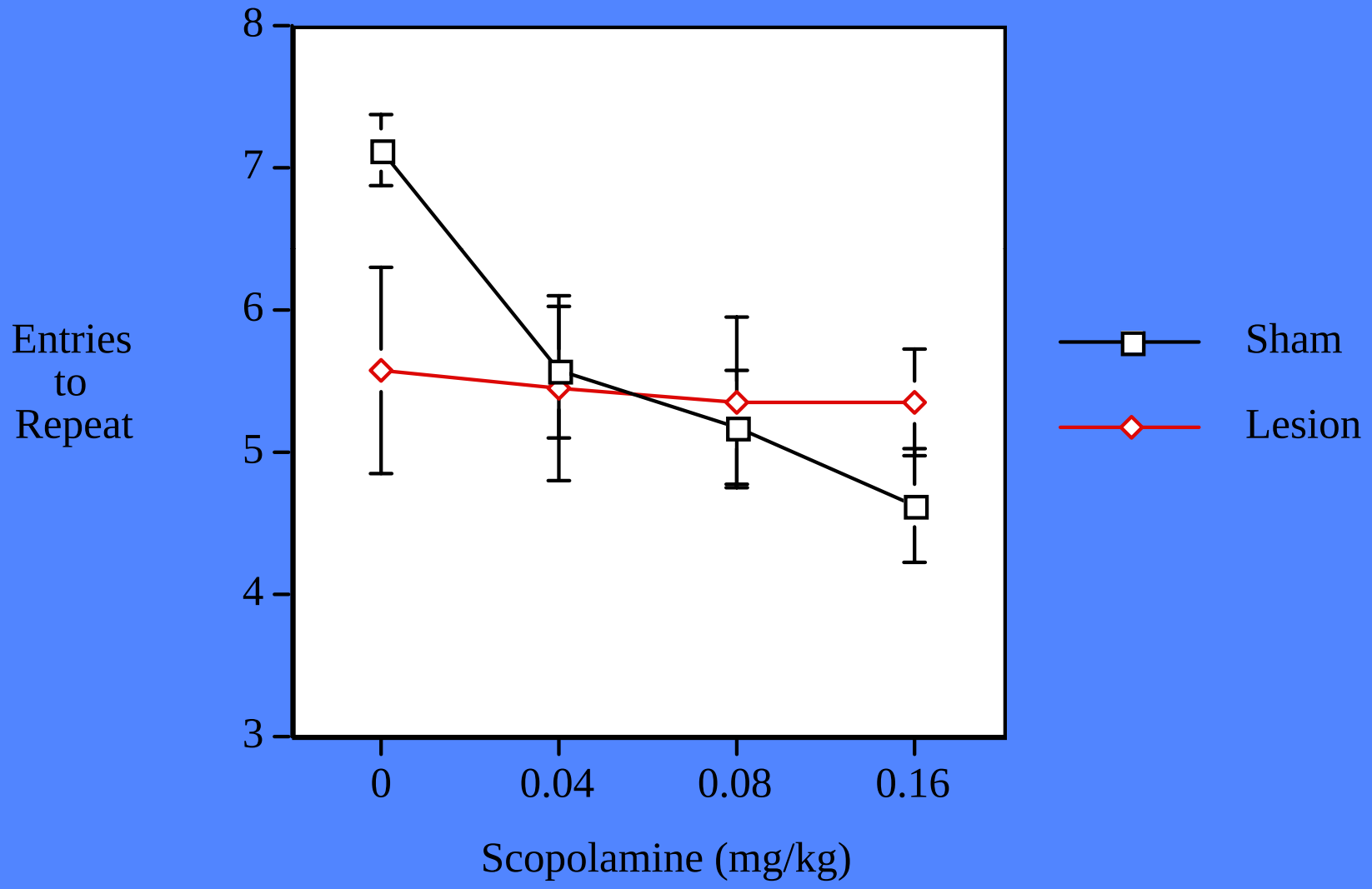
Theoretical Triphasic Dose-Effect Function of Lethal Risk from Alcohol Intoxication



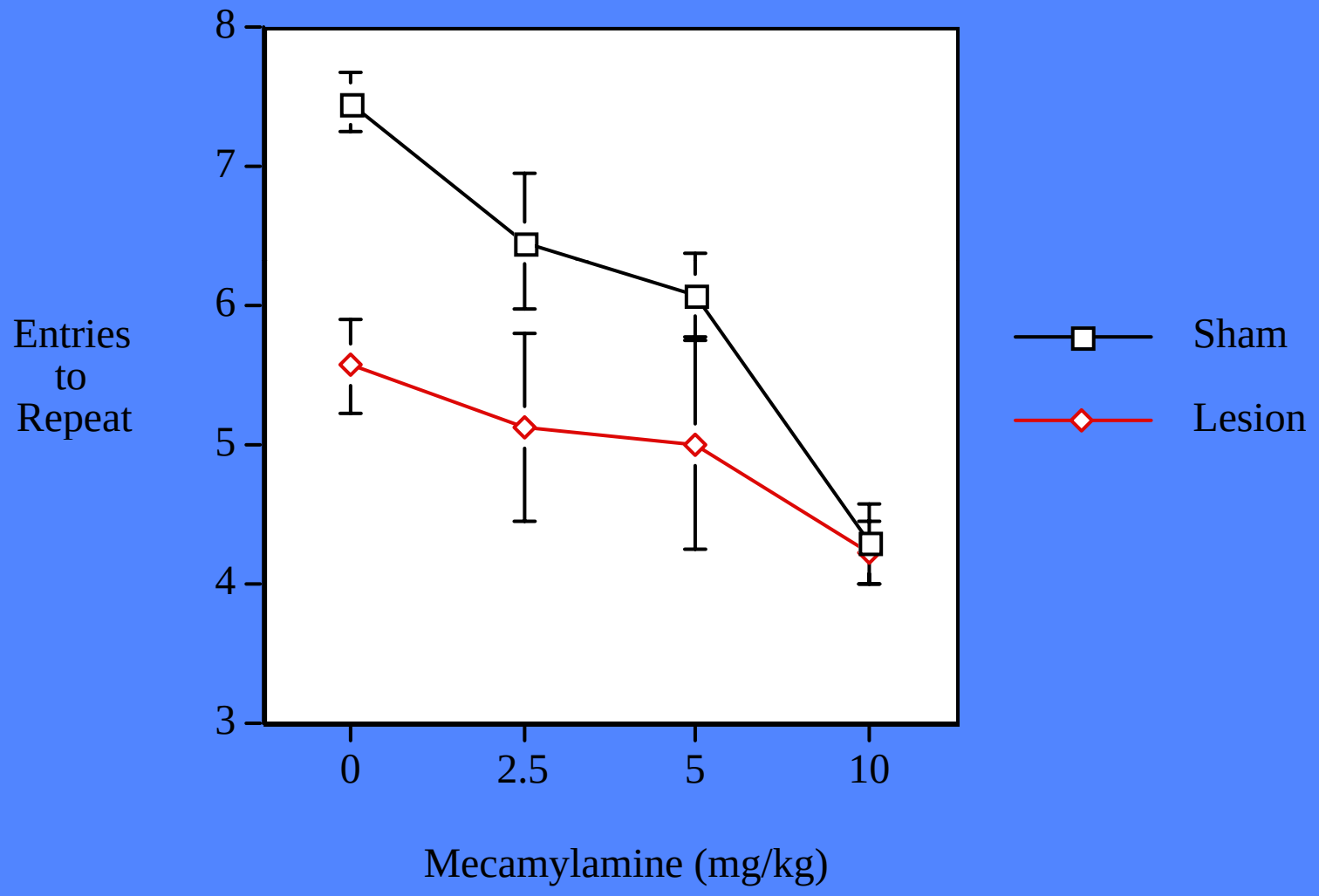
Unilateral and Bilateral Neonatal Ventral Hippocampal Lesion Effects on Radial-Arm Maze Acquisition

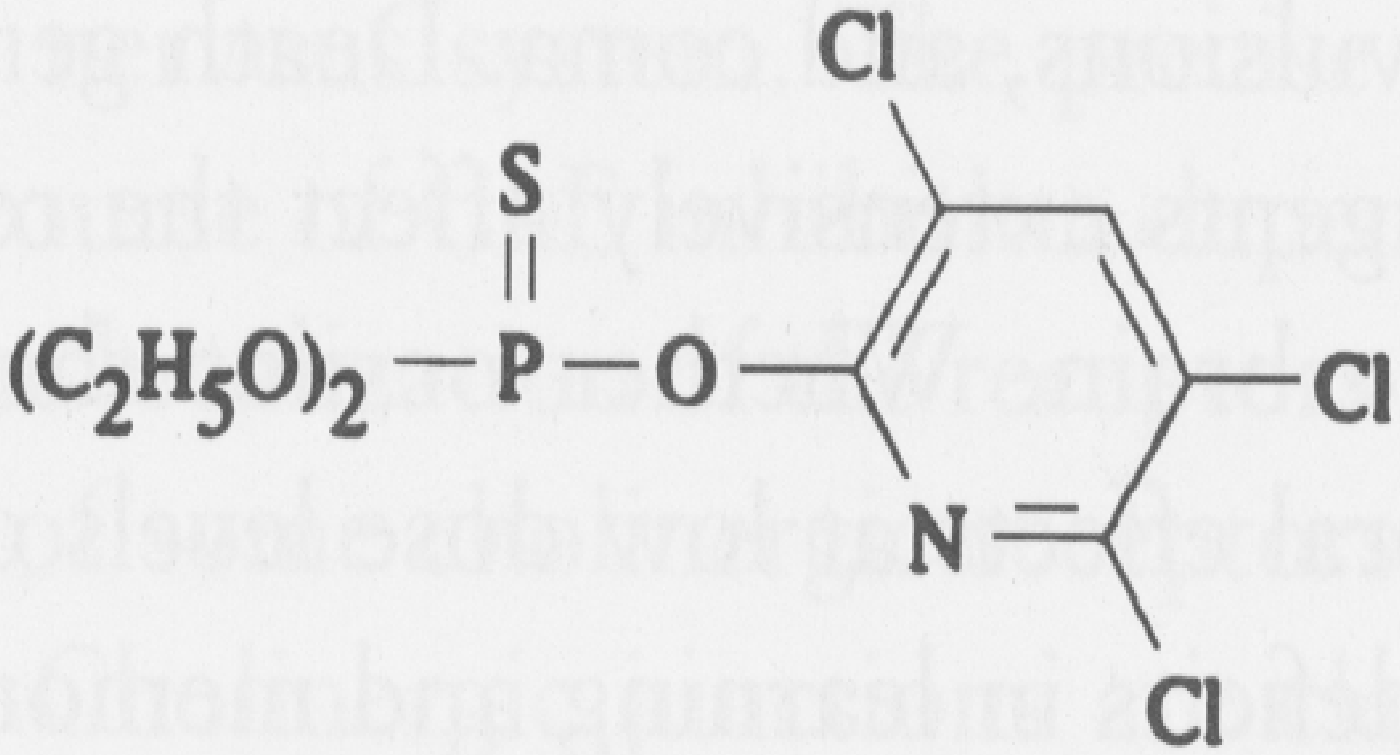


Neonatal Hippocampal Lesions and Scopolamine Effects on Radial-Arm Maze Performance



Neonatal Hippocampal Lesions and Mecamylamine Effects on Radial-Arm Maze Performance





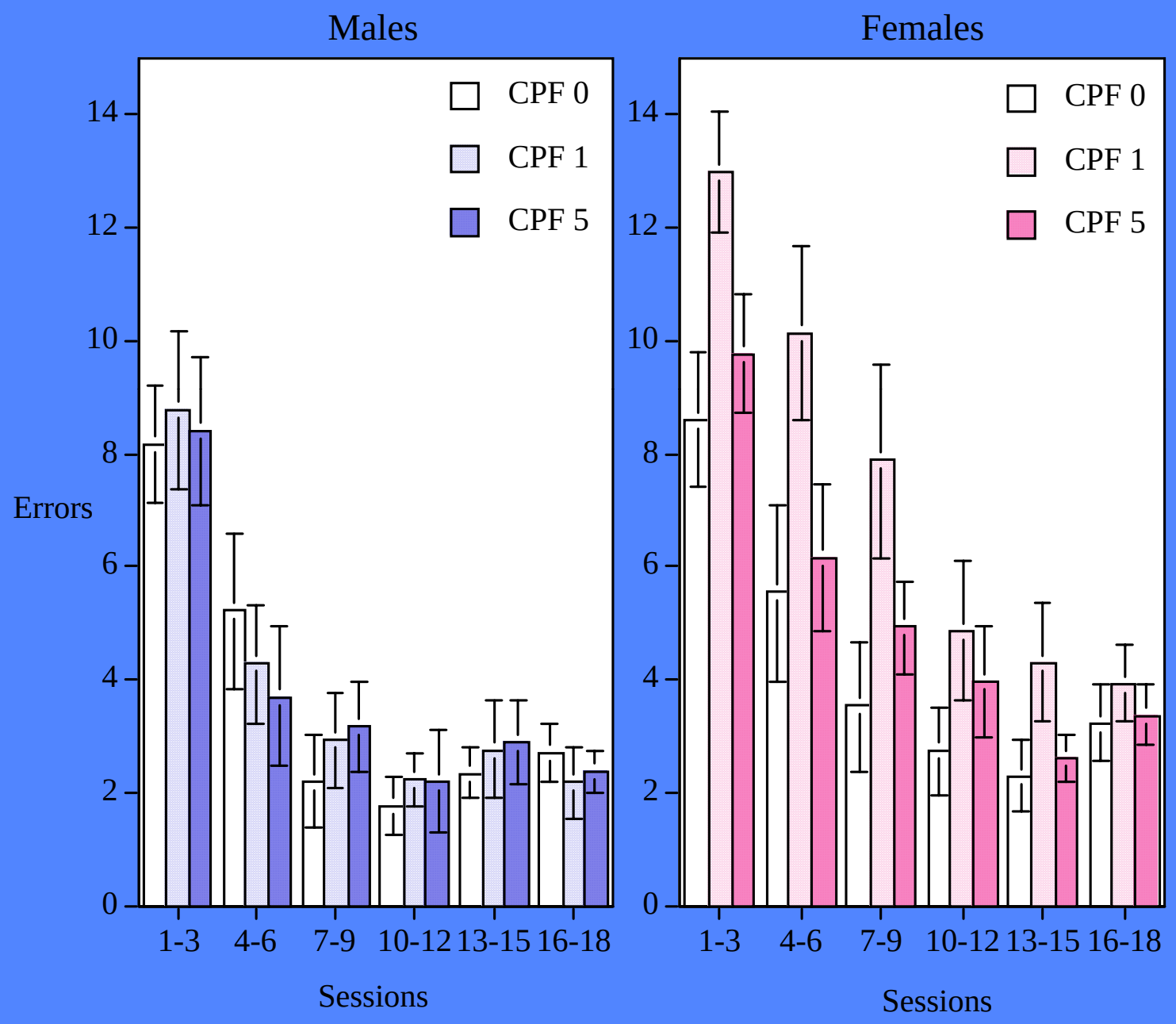
Chlorpyrifos

Goals of the Research

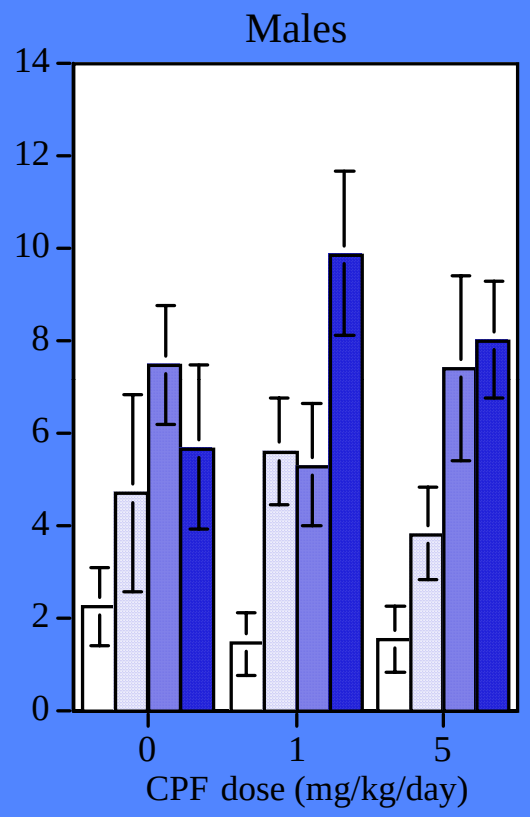
- Determine the persisting neurobehavioral effects of postnatal CPF exposure in rats
- Compare the effects of early and late postnatal CPF exposure
- Identify sex differences in response
- Develop methods for neurobehavioral assessment in Zebrafish
- Study CPF mechanisms in Zebrafish

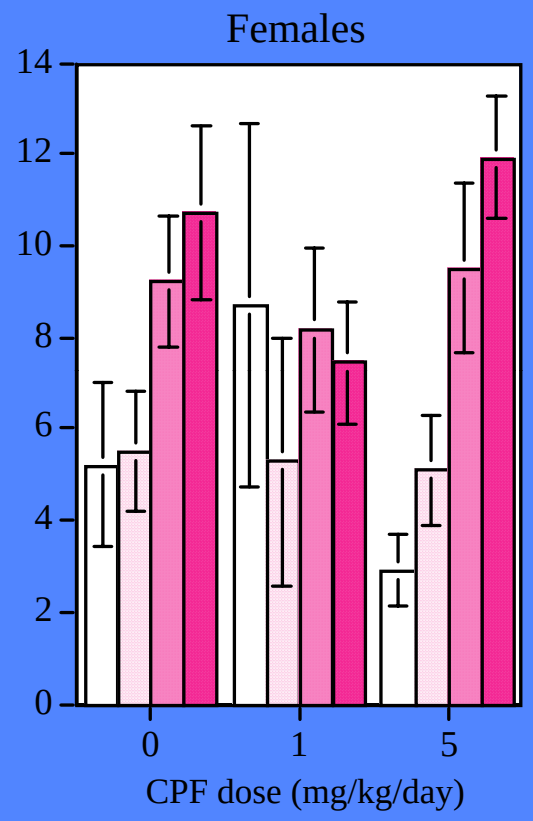

16
1
2
14
13
12
10
9
8
7
6

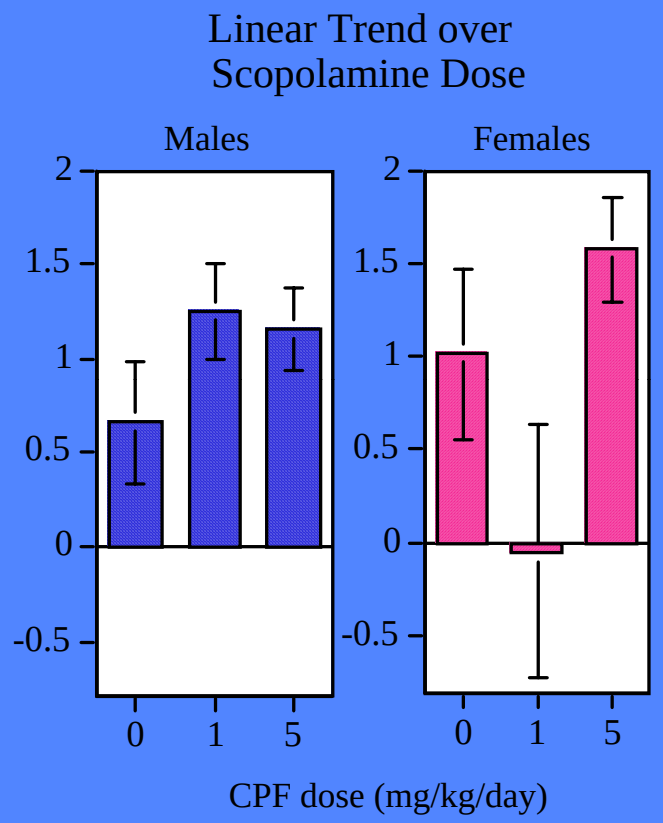
Prenatal Chlorpyrifos Effects on 16-Arm Radial Maze Acquisition Working Memory Errors



Prenatal Chlorpyrifos Effects on 16-Arm Maze Performance
Scopolamine Challenge: Working Memory







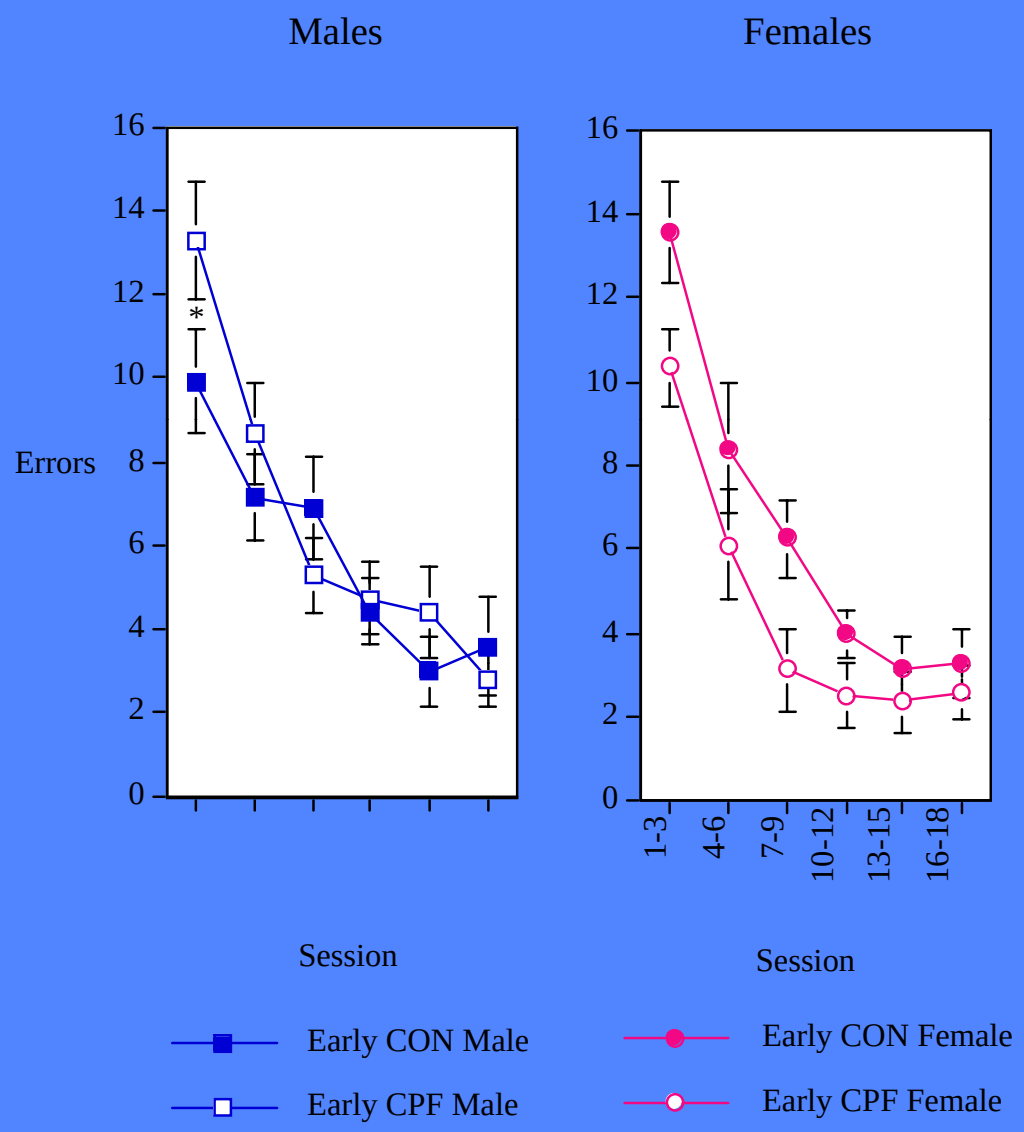
Scopolamine

- 0 mg/kg
- 0.04 mg/kg
- 0.08 mg/kg
- 0.16 mg/kg

Scopolamine

- 0 mg/kg
- 0.04 mg/kg
- 0.08 mg/kg
- 0.16 mg/kg

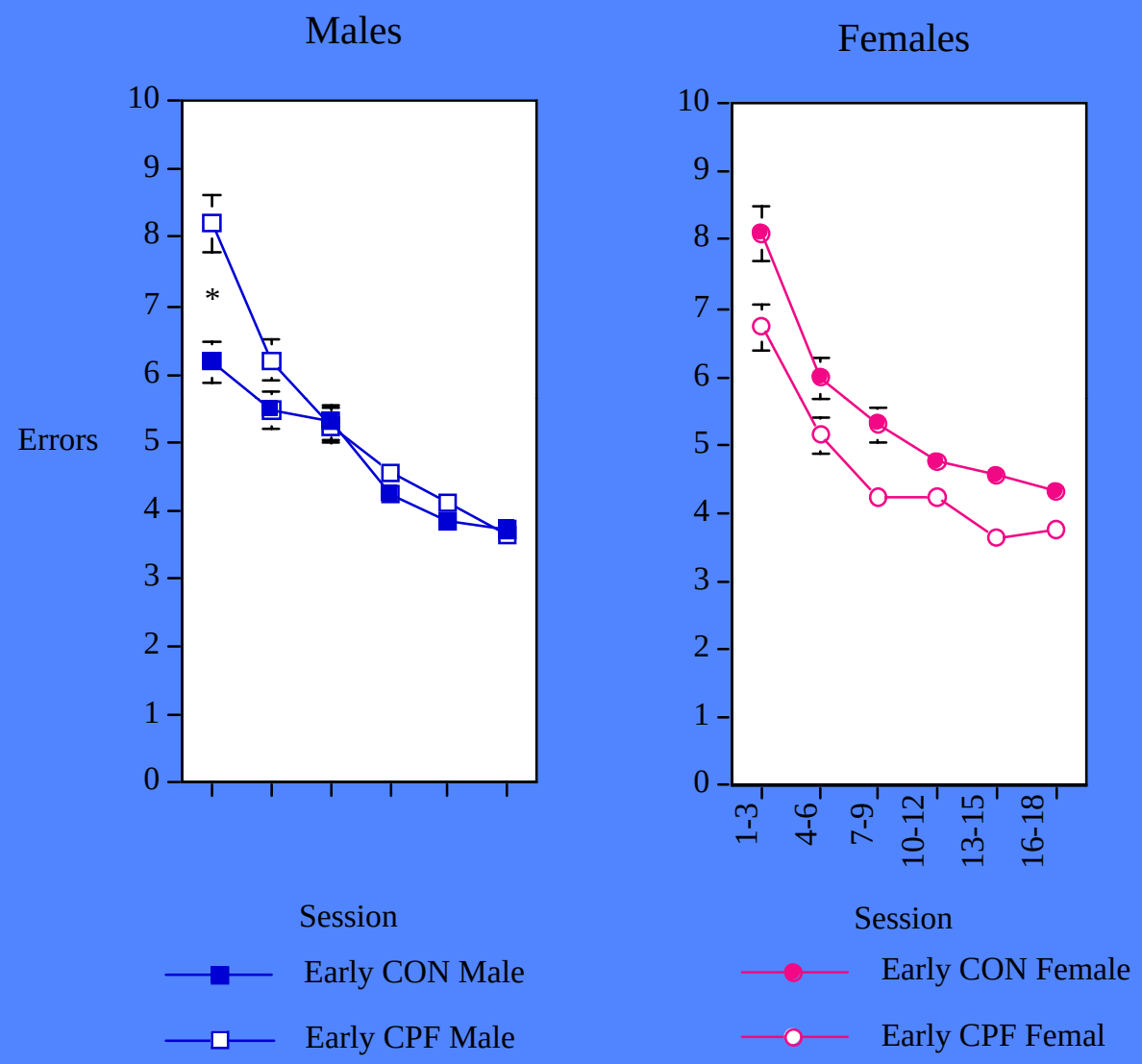
Persistent Early Chlorpyrifos (1 mg/kg/day PND 1-4) Effects on Working Memory Errors in the 16-Arm Radial Maze



Male Early Con vs. CPF
*p<0.05 sessions 1-3

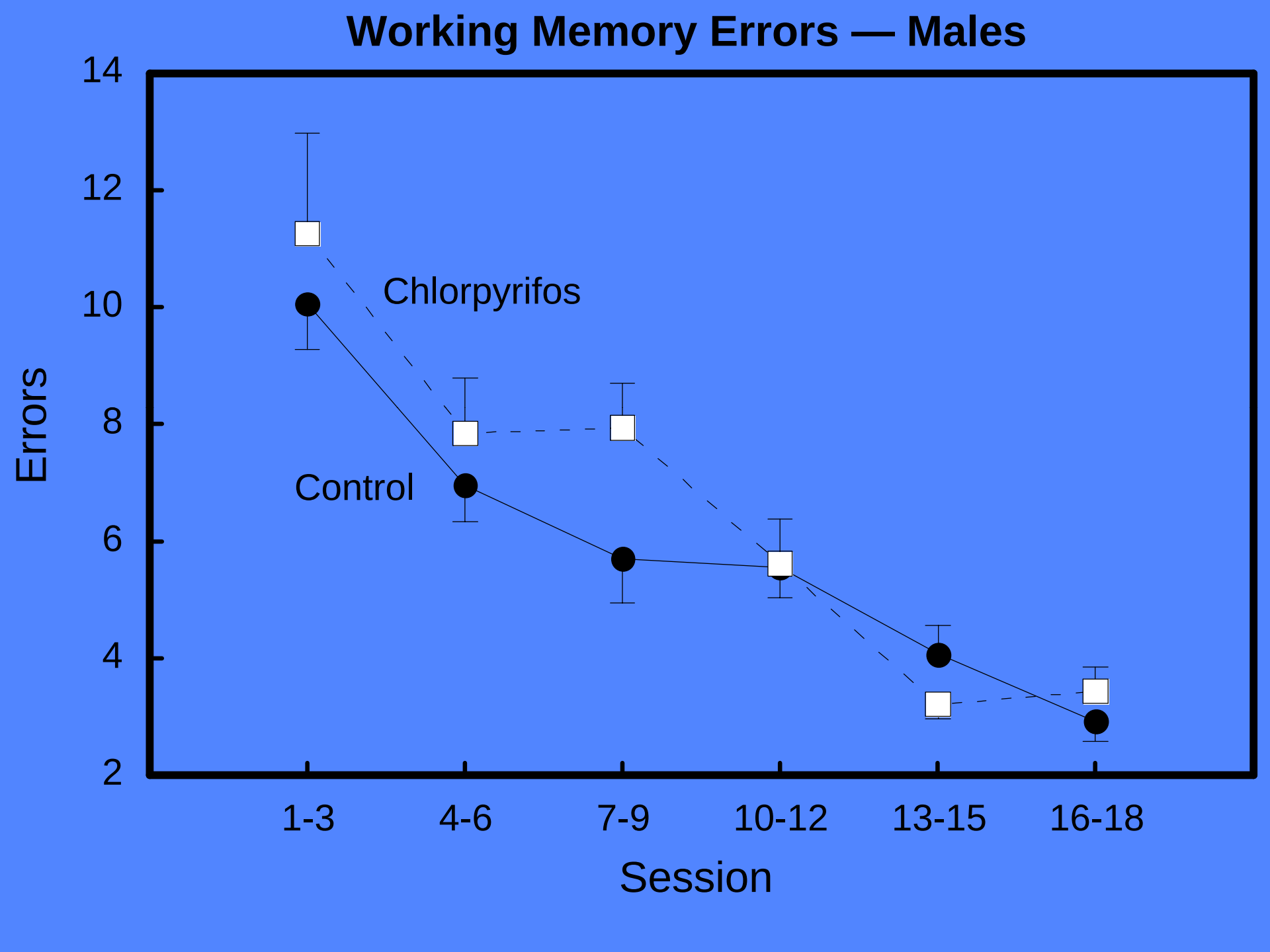
Female Early Con vs. CPF
p<0.05 over all sessions

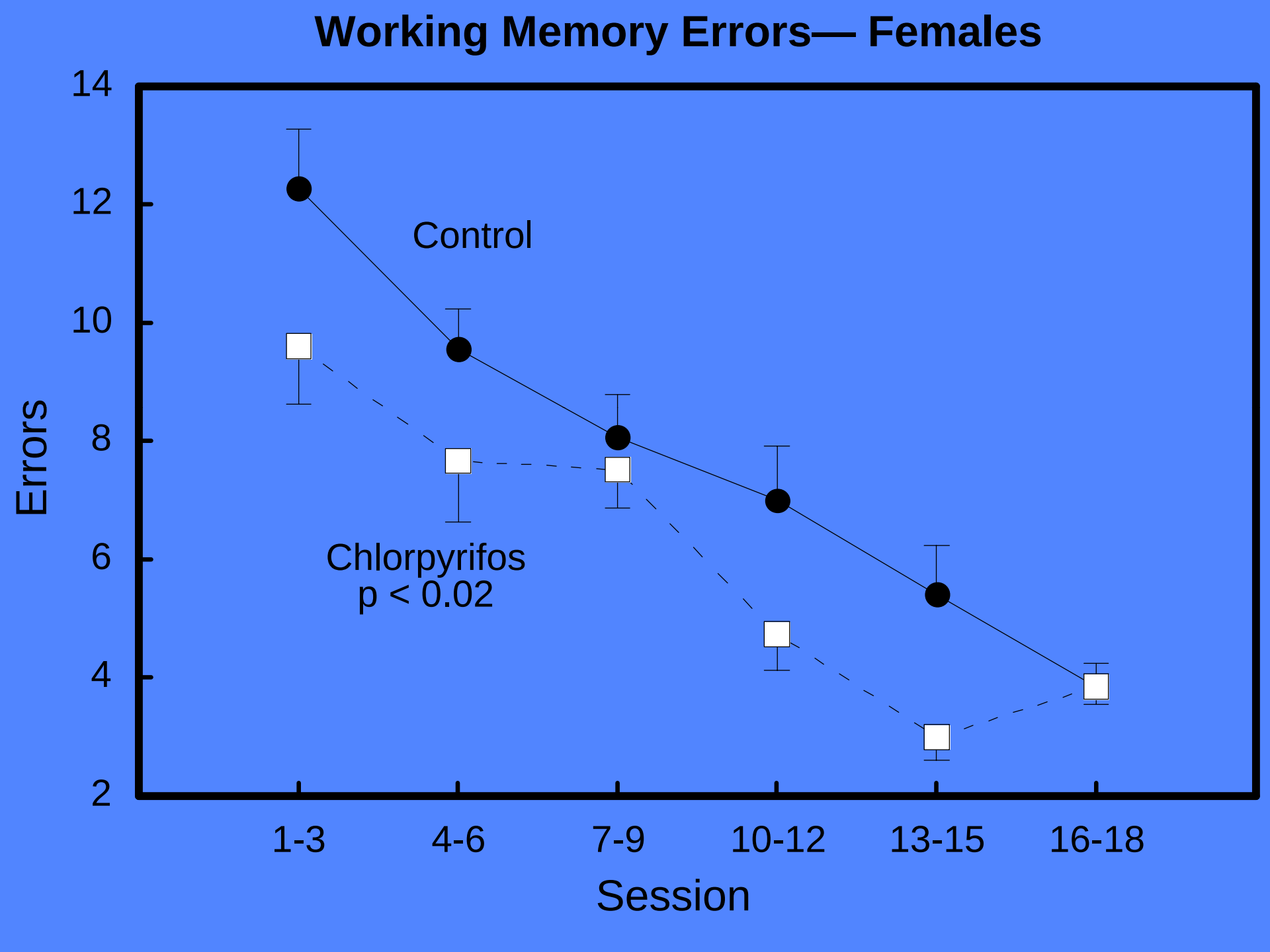
Persistent Early Chlorpyrifos (1 mg/kg/day PND 1-4) Effects on Reference Memory Errors in the 16-Arm Radial Maze



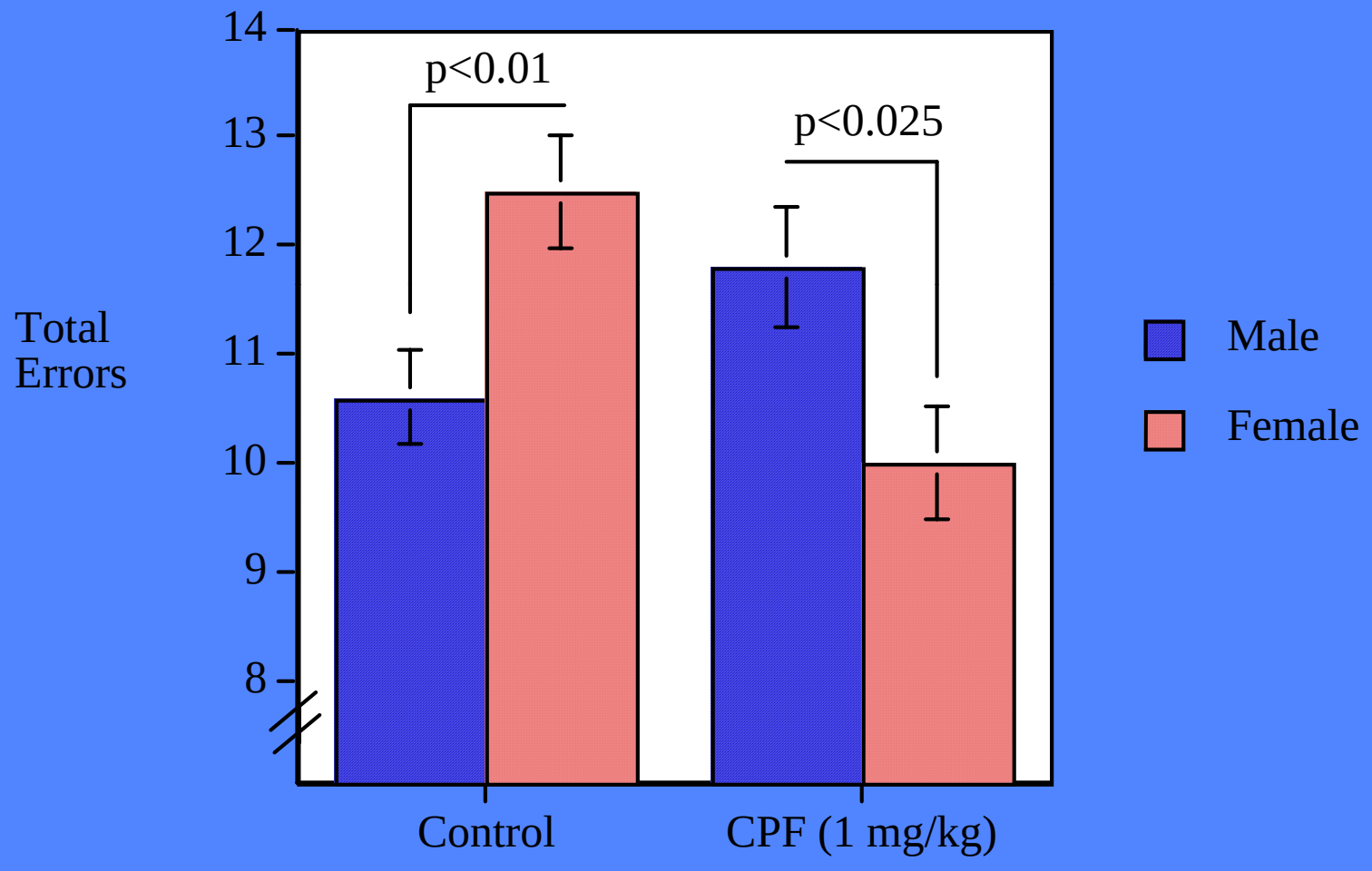
Male Early Con vs. CPF
*p<0.025 sessions 1-3

Female Early Con vs. CPF
p<0.05 over all sessions


Working Memory Errors — Males
14
12
10
8
6
4
2
Errors
Chlorpyrifos
Control
1-3
4-6
7-9
10-12
13-15
16-18
Session

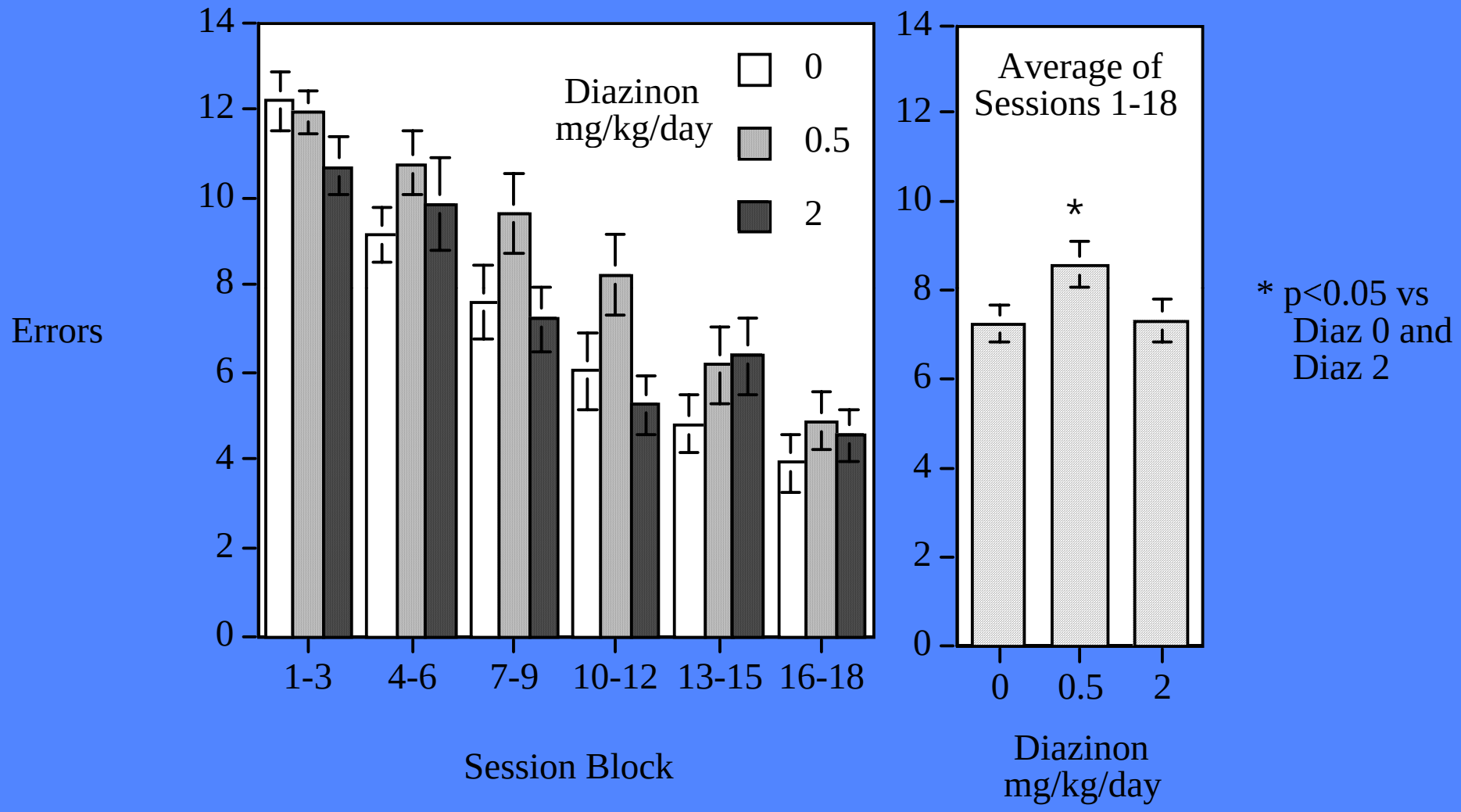

Working Memory Errors— Females
14
12
10
8
6
4
2
Errors
Control
Chlorpyrifos
p < 0.02
1-3
4-6
7-9
10-12
13-15
16-18
Session

Early Postnatal Chlorpyrifos Exposure Reverses Normal Sex Differences in Radial-Arm Maze Performance

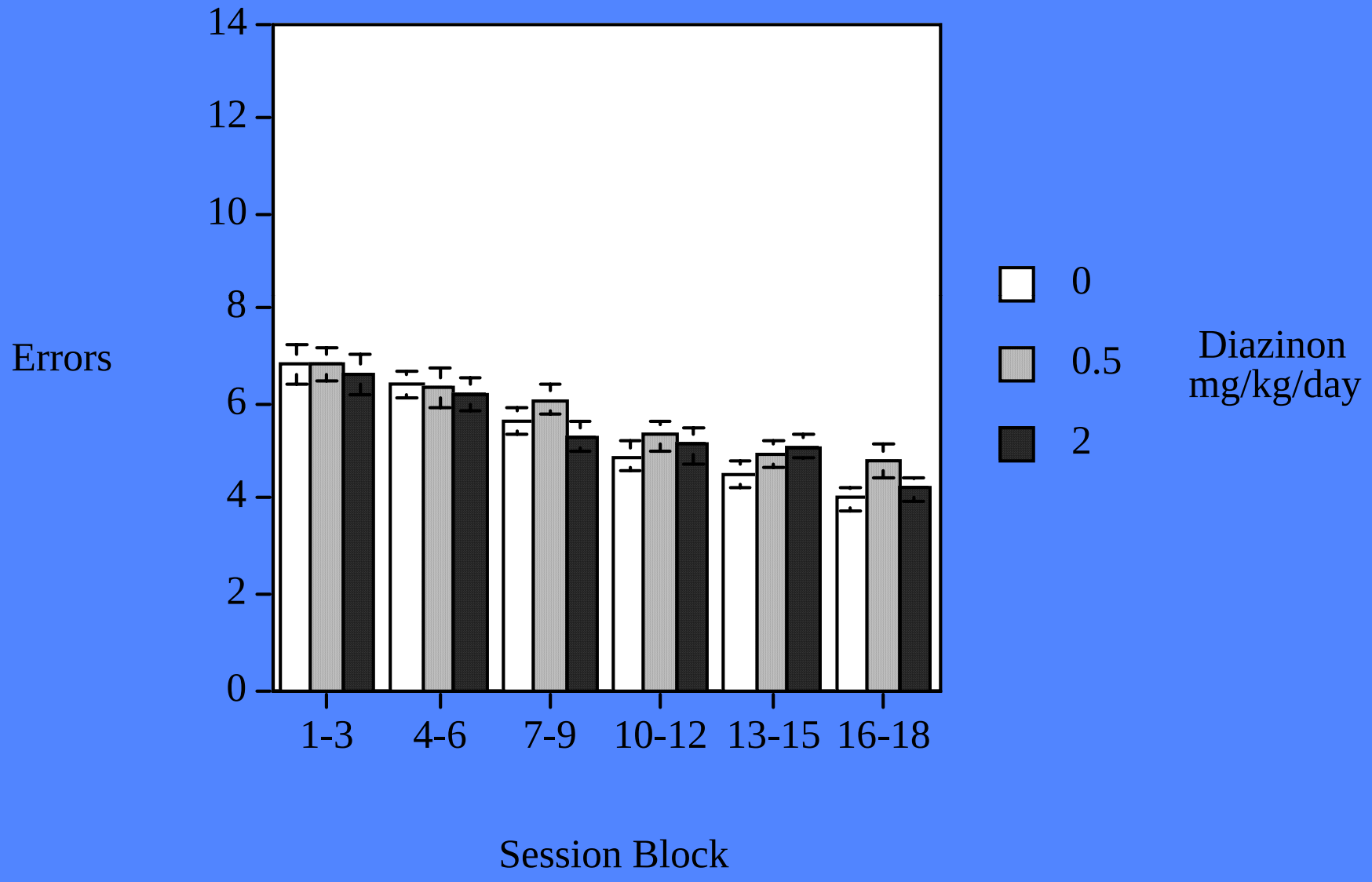


Postnatal Days 1-4 Treatment

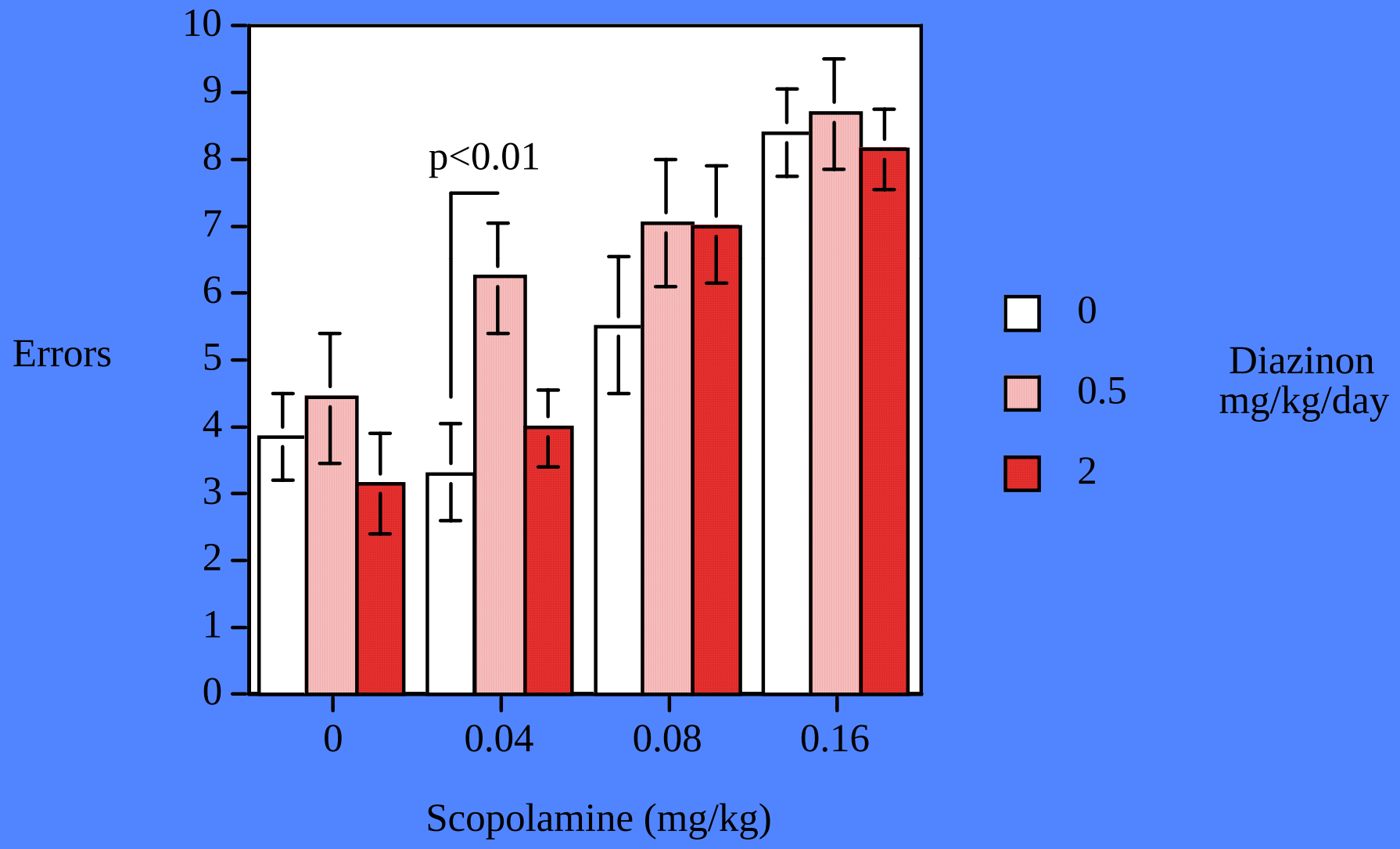
Early Postnatal (PND 1-4) Diazinon Exposure Effects on Radial-Arm Maze Working Memory Performance in Adulthood

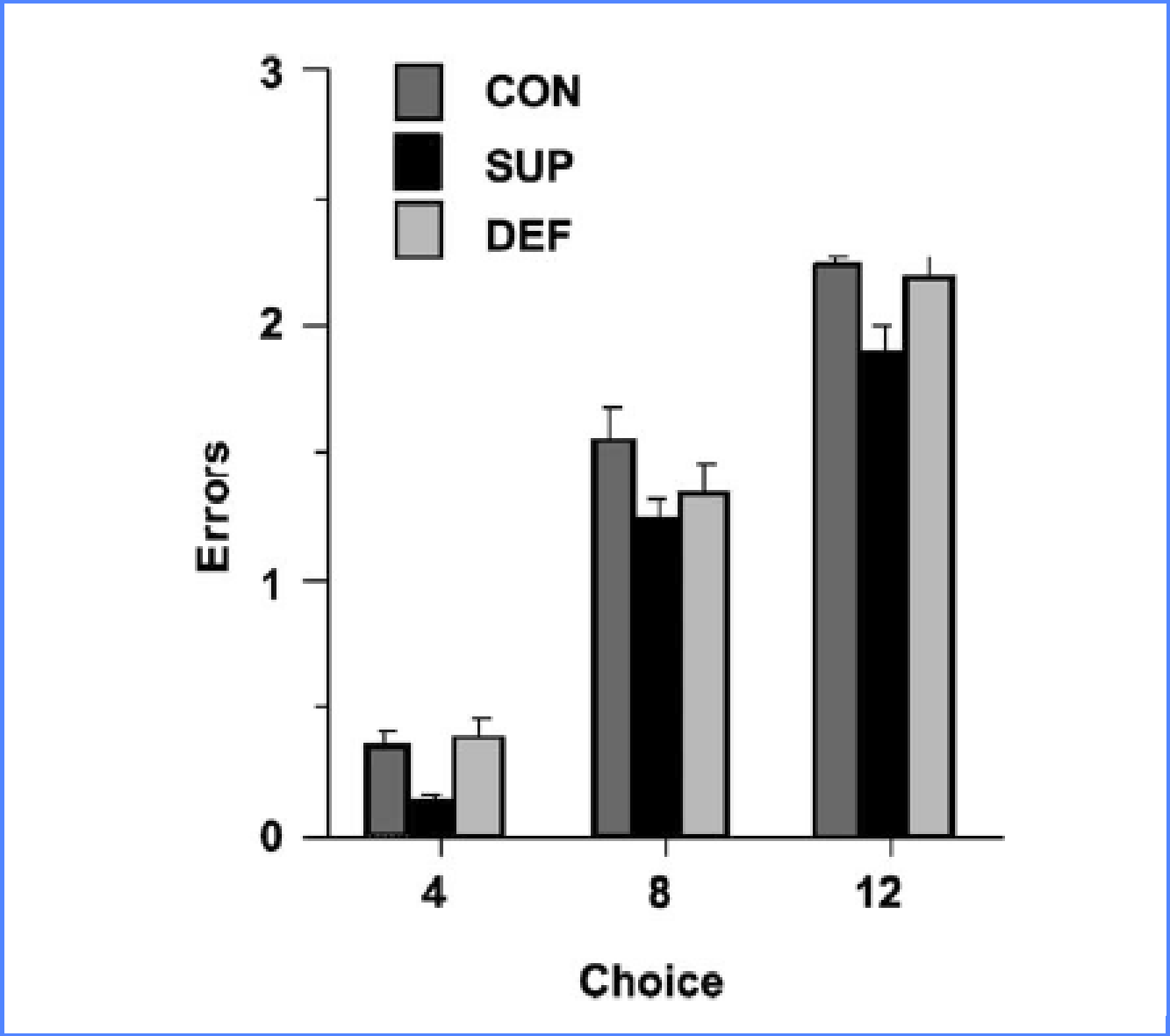


Early Postnatal (PND 1-4) Diazinon Exposure Effects on Radial-Arm Maze Reference Memory Performance in Adulthood

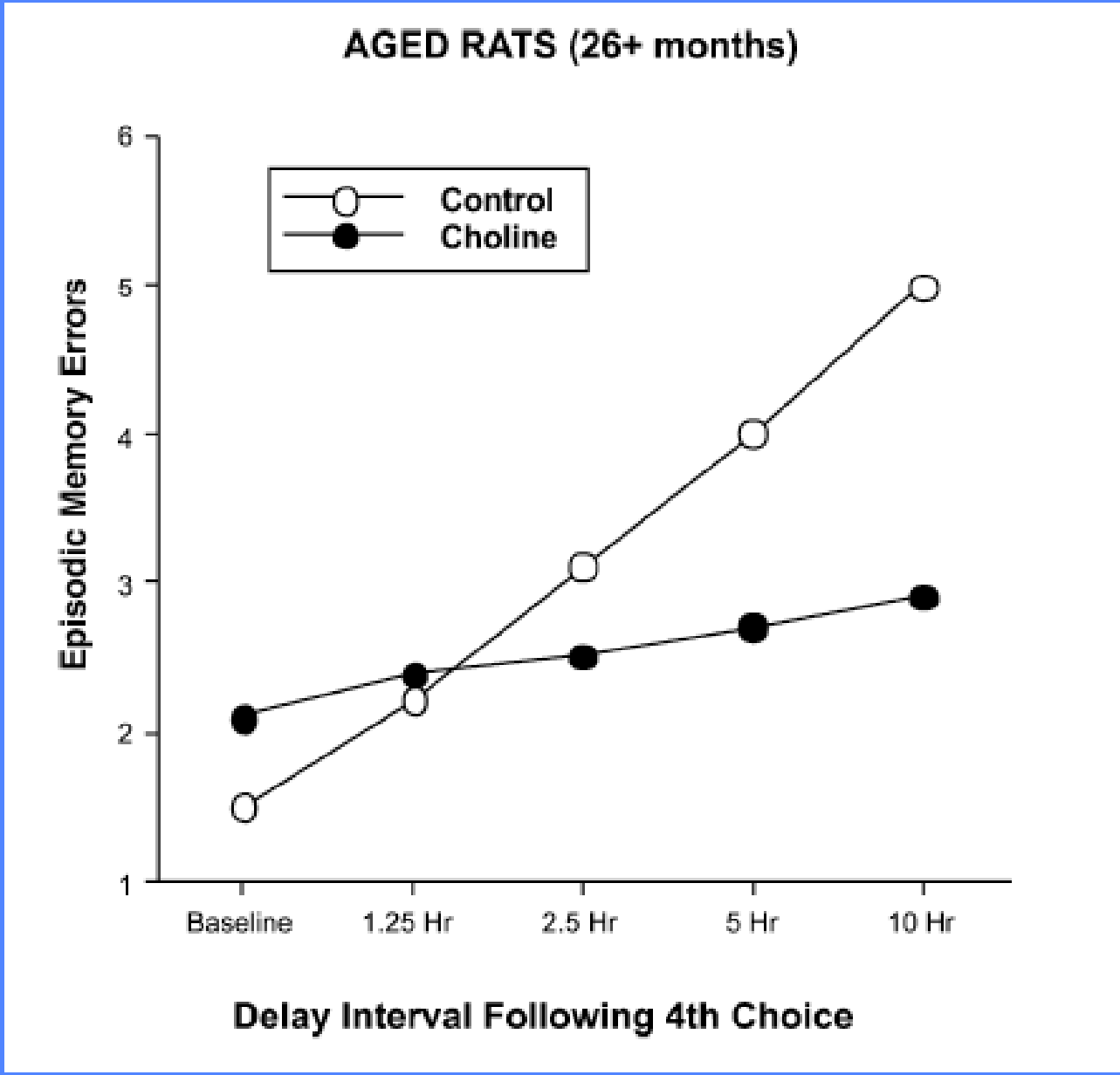


Early Postnatal (PND 1-4) Diazinon Exposure Effects on Radial-Arm Maze Working Memory Performance with Scopolamine Challenge



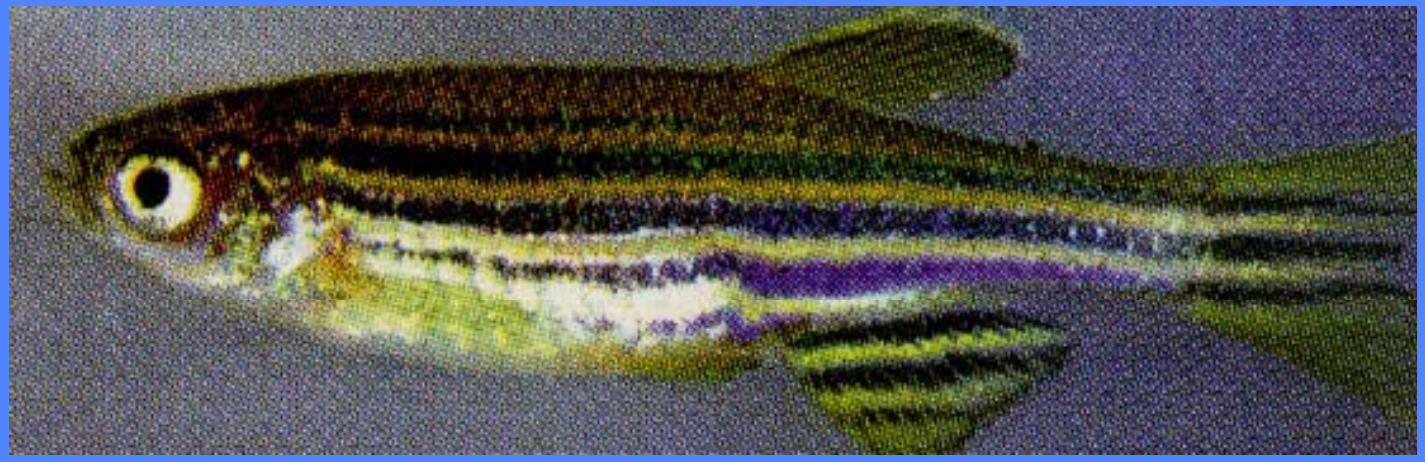


Meck and Williams, Neurosci Biobehav Rev, 2003



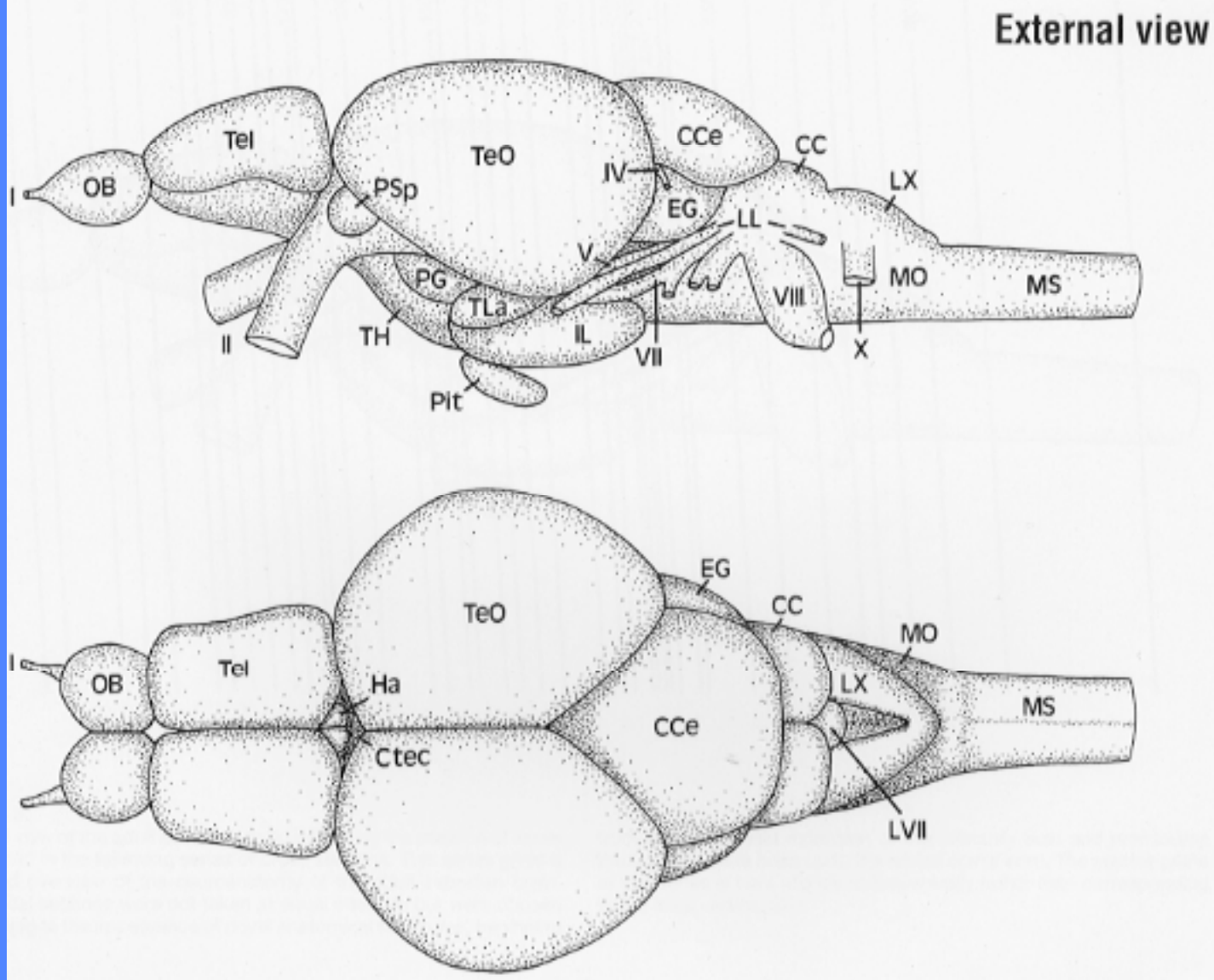
Meck and Williams, Neurosci Biobehav Rev, 2003

Adult Zebrafish



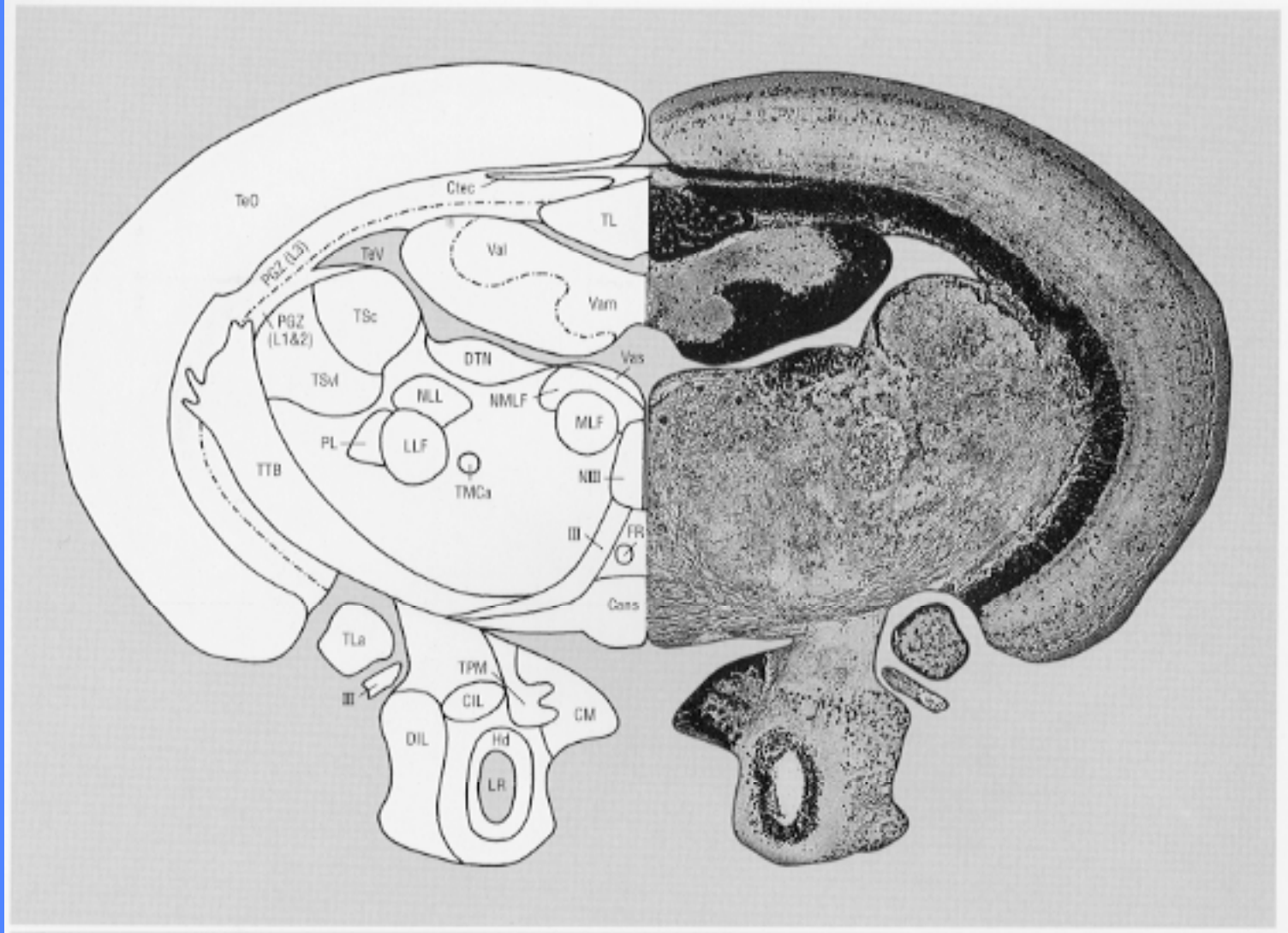
The brain of the zebrafish *Danio rerio*: a neuroanatomical atlas

Wullimann et al., 1996



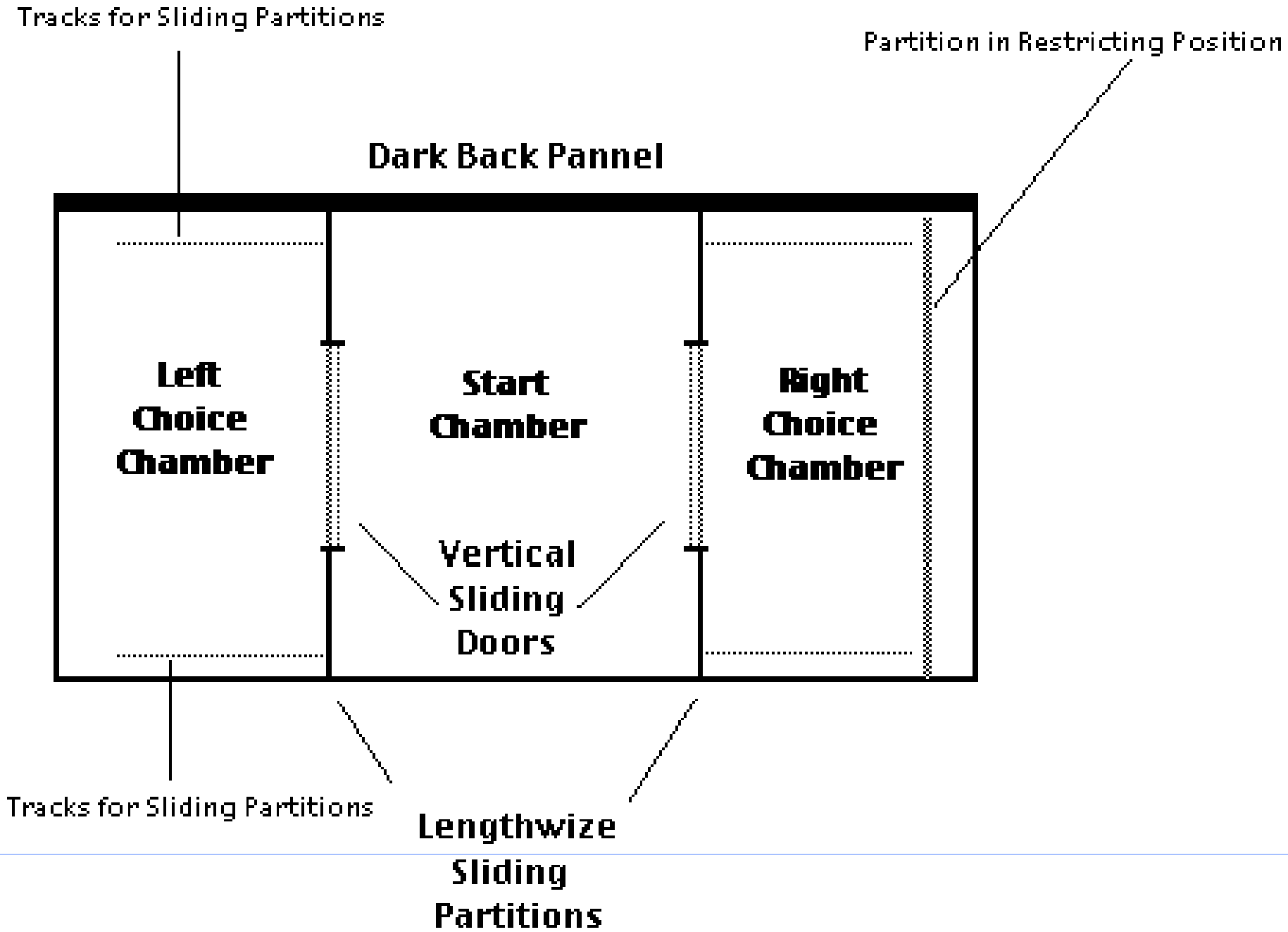
Wullimann et al., 1996

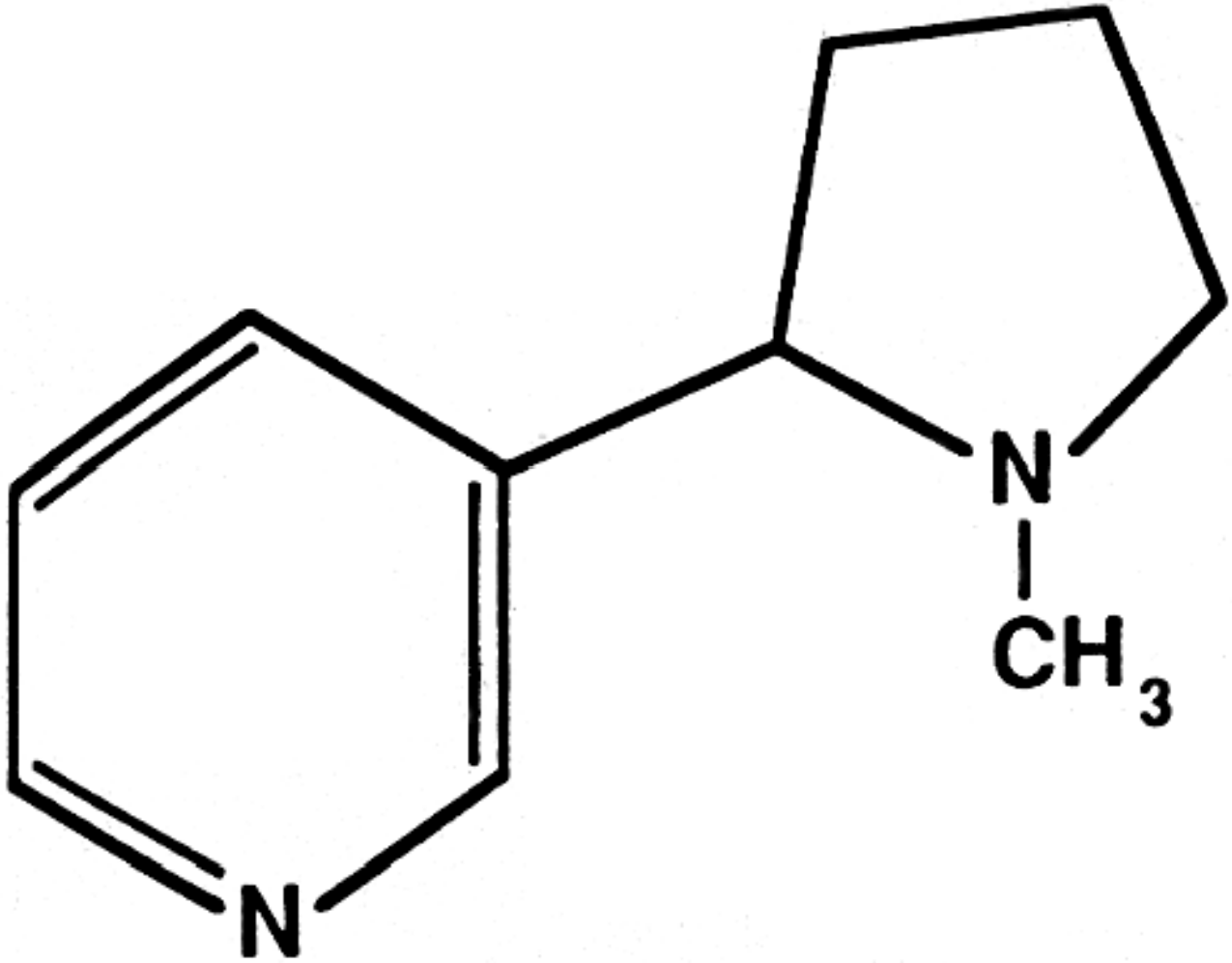
Cross Section 179



200 µm

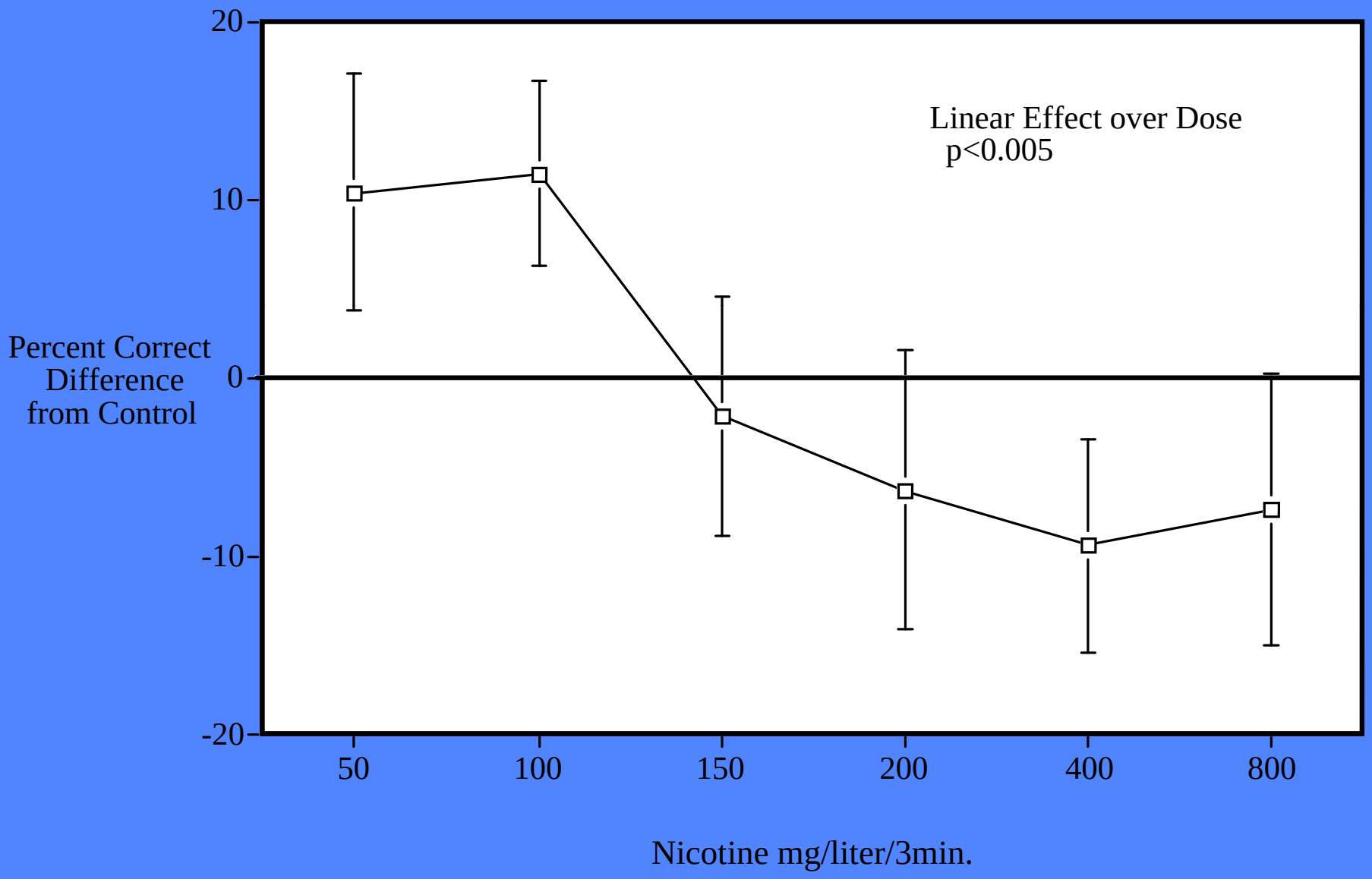
179

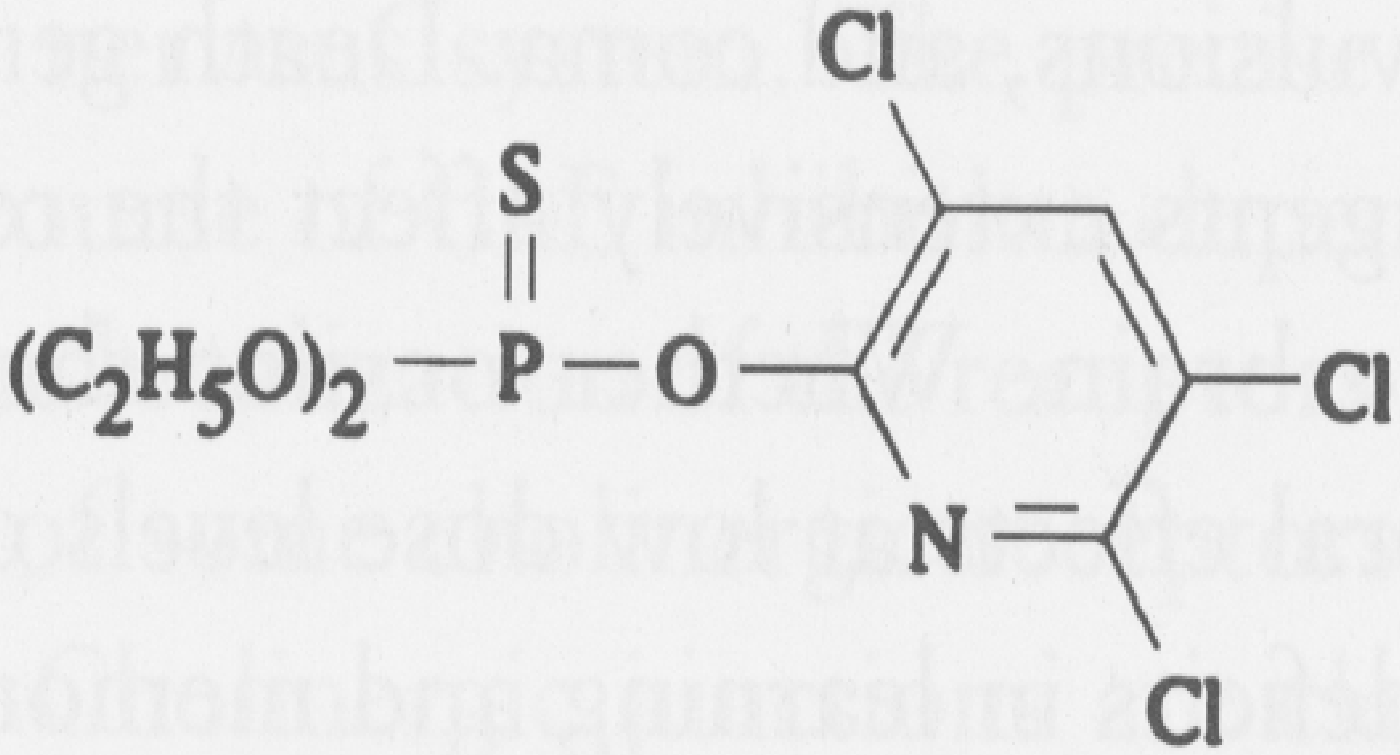

Tracks for Sliding Partitions
Partition in Restricting Position
Dark Back Pannel
Left Choice Chamber
Start Chamber
Right Choice Chamber
Vertical Sliding Doors
Tracks for Sliding Partitions
Lengthwize Sliding Partitions



NICOTINE

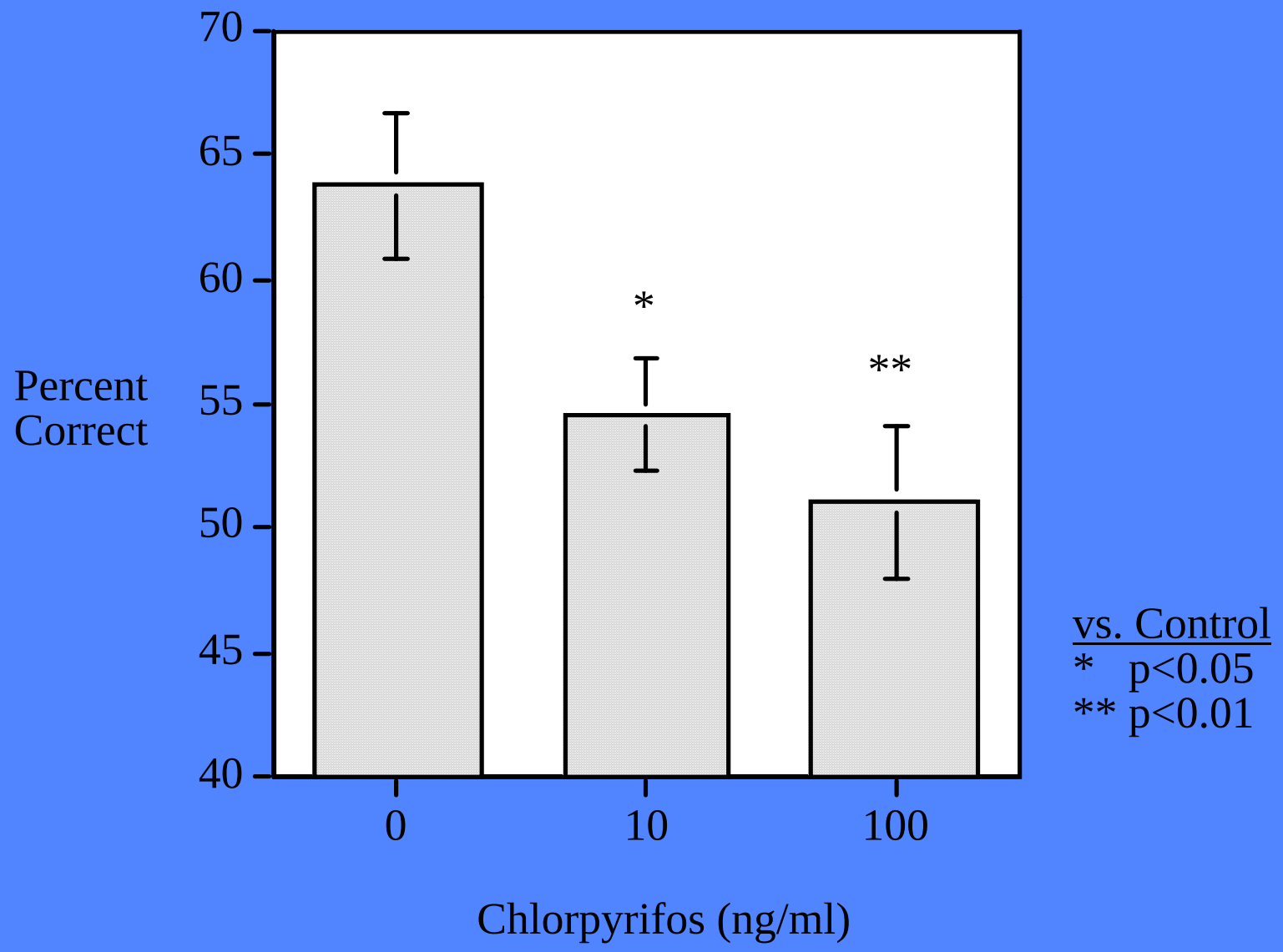
Nicotine Effects on Delayed Spatial Alternation in Zebrafish
Percent Correct



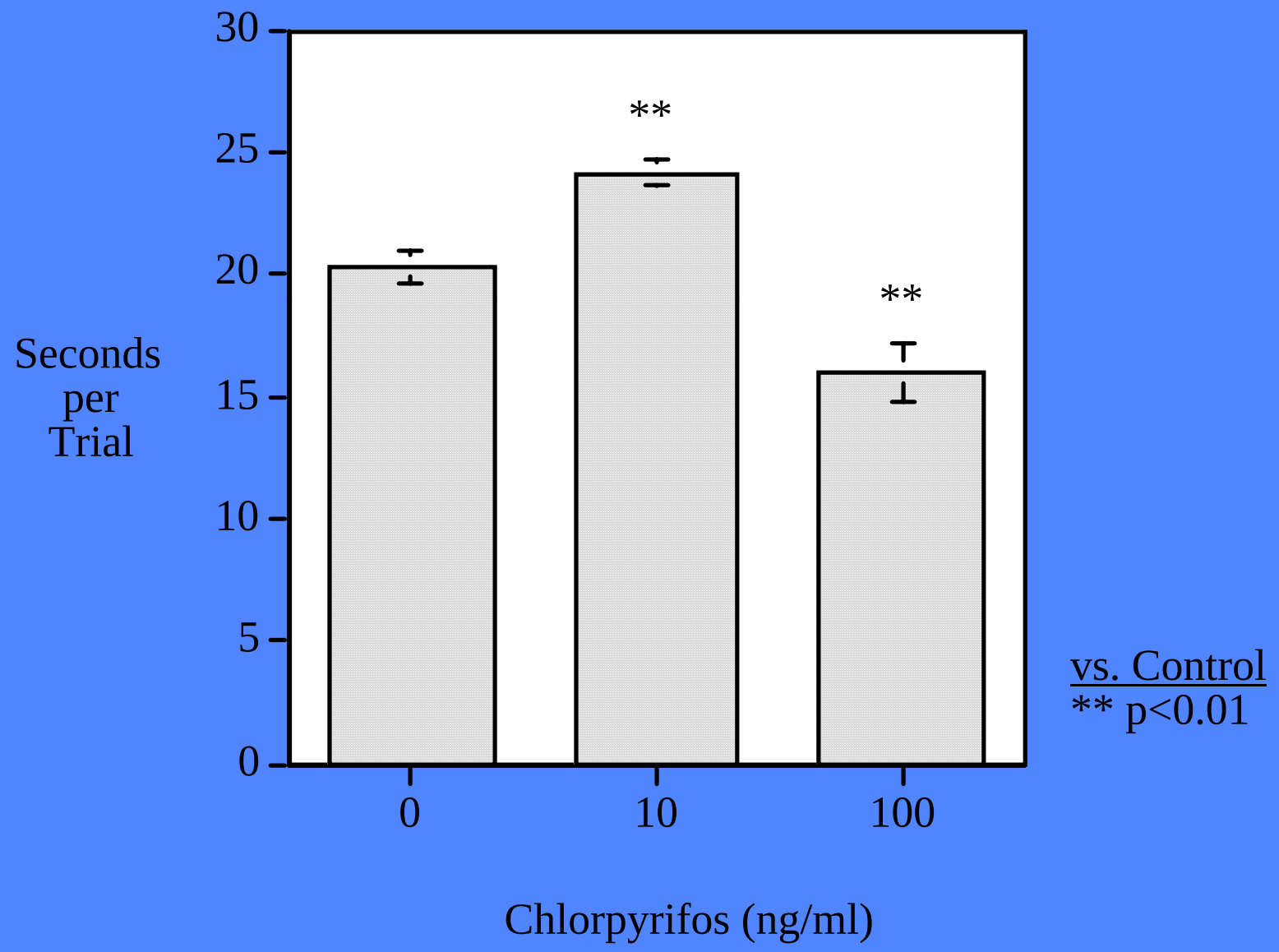


Chlorpyrifos

Developmental Chlorpyrifos Exposure Effects on Average Choice Accuracy



Developmental Chlorpyrifos Exposure Effects on Average Response Latency

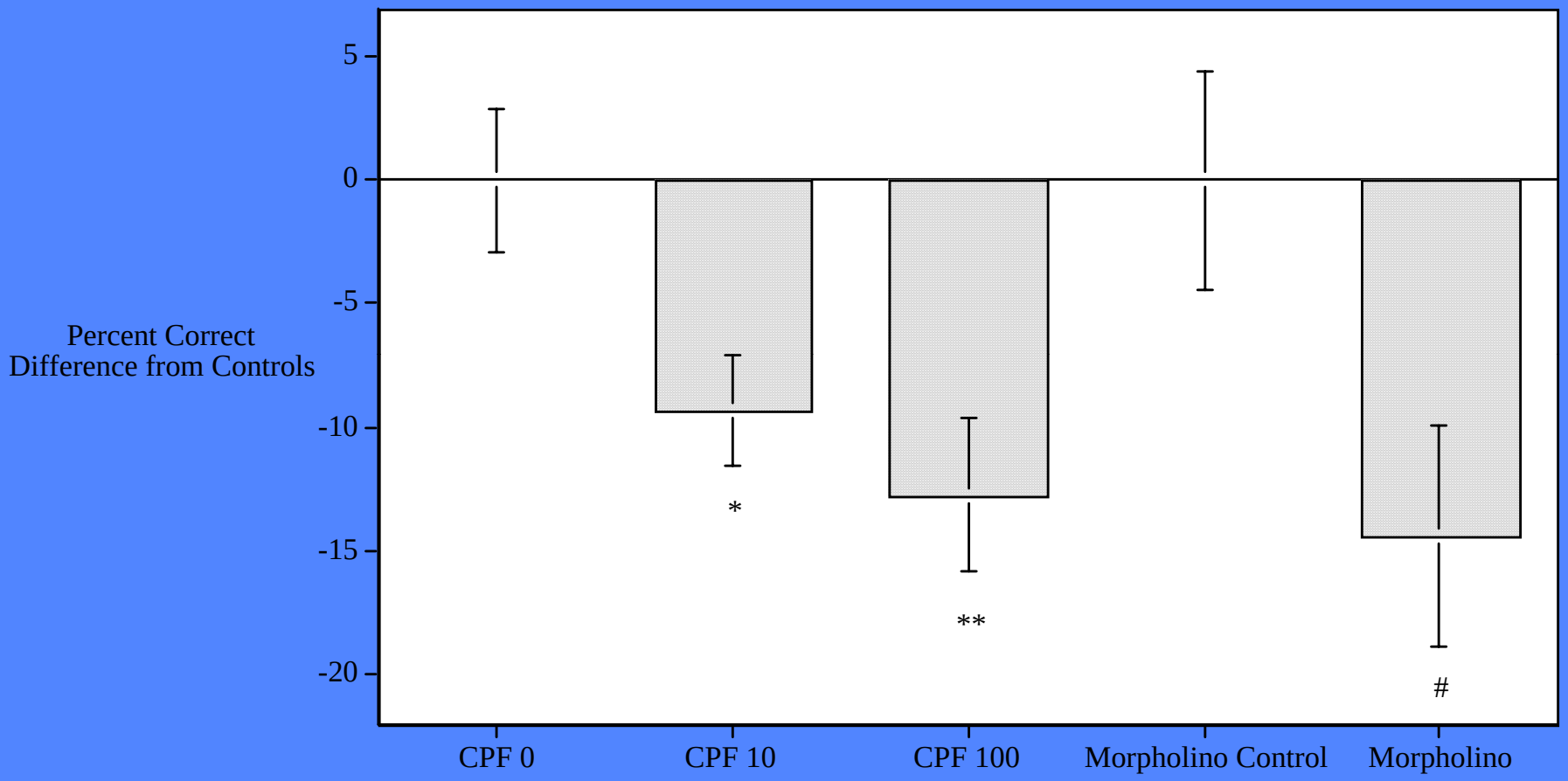


Morpholinos

Molecular suppression

of acetylcholinesterase

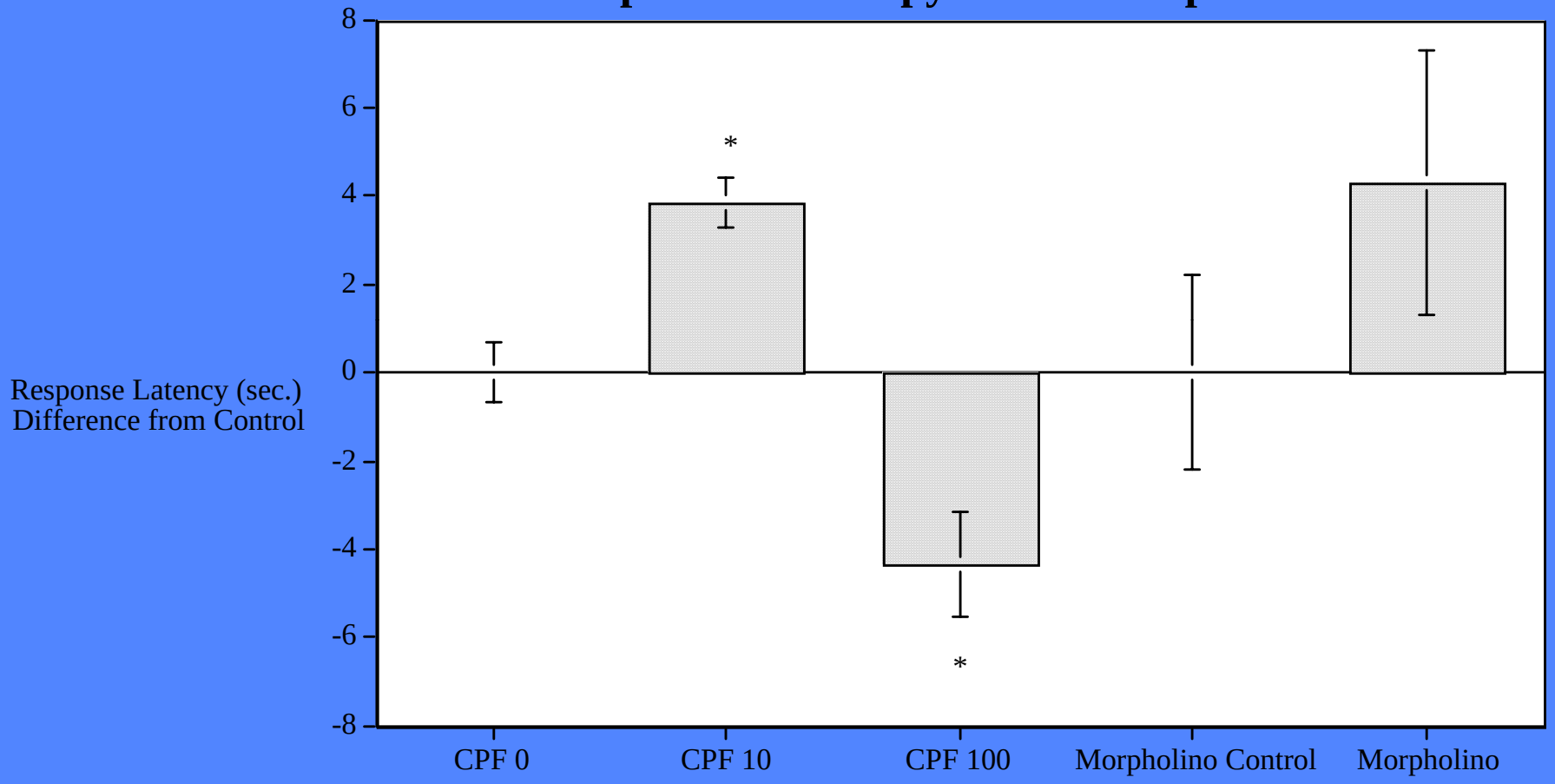
Delayed Spatial Alternation Choice Accuracy with Developmental Chlorpyrifos or Morphoino Zebrafish



vs. CPF 0
* p<0.05
** p<0.01

vs. Morpholino Control
# p<0.025

Delayed Spatial Alternation Response Latency with Developmental Chlorpyrifos or Morphoino Zebrafish



* p<0.01 vs. CPF 0

Conclusions

In both rats and zebrafish nonmonotonic dose effect functions of OPs can be seen.

Impairments at doses lower than those that cause no apparent effect can cause dysfunction.

Recommendation

When tracking the decreasing effects of decreasing doses of a toxicant one must investigate doses below the initial intersection with no effect because multiple mechanisms of effect can induce nonmonotonic dose effect functions.

Future Studies

Other OP’s

Affective Function

Neural Bases

Pharmacological Probes

Interaction Studies

Rapid Throughput Tests

Collaborators

Dr. Ted Slotkin

Dr. Fred Seidler

Dr. Elwood Linney

Dr. Amir Rezvani

Channelle Christopher

Laura Icenogle

Justin Aldrich

Paul Blackwelder

Research Support

Superfund Basic Research Center

Map of North America in 1650