

Placental Transport of Brevetoxin in Rodents: Public Health Implications

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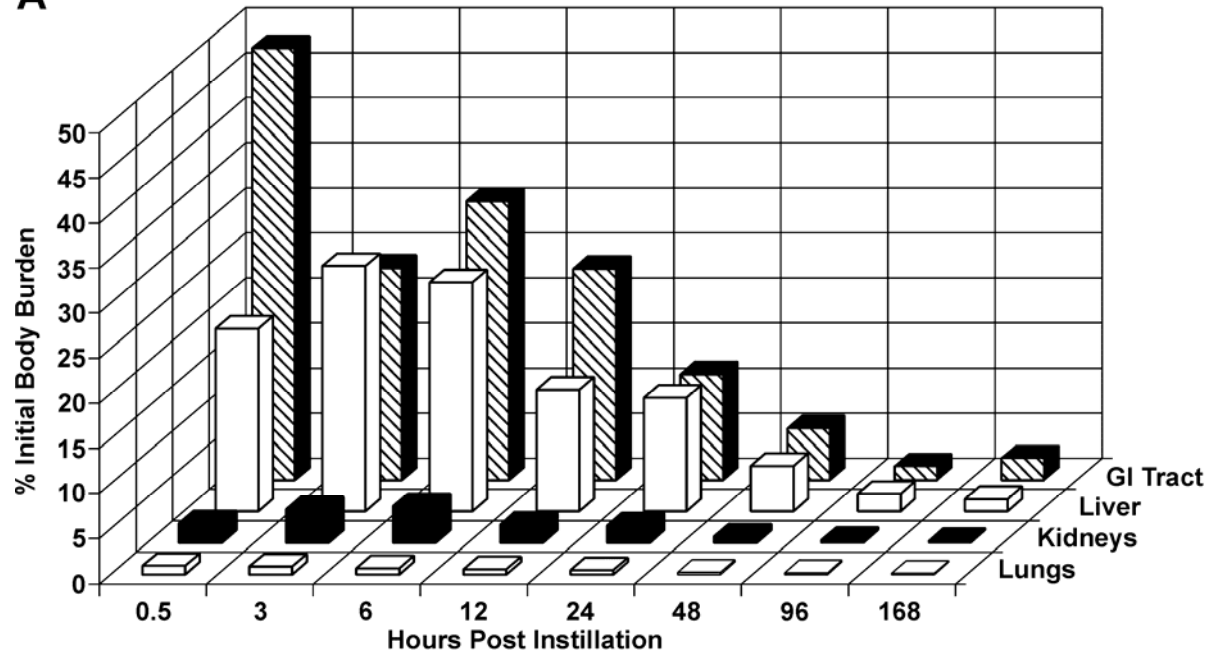
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Background

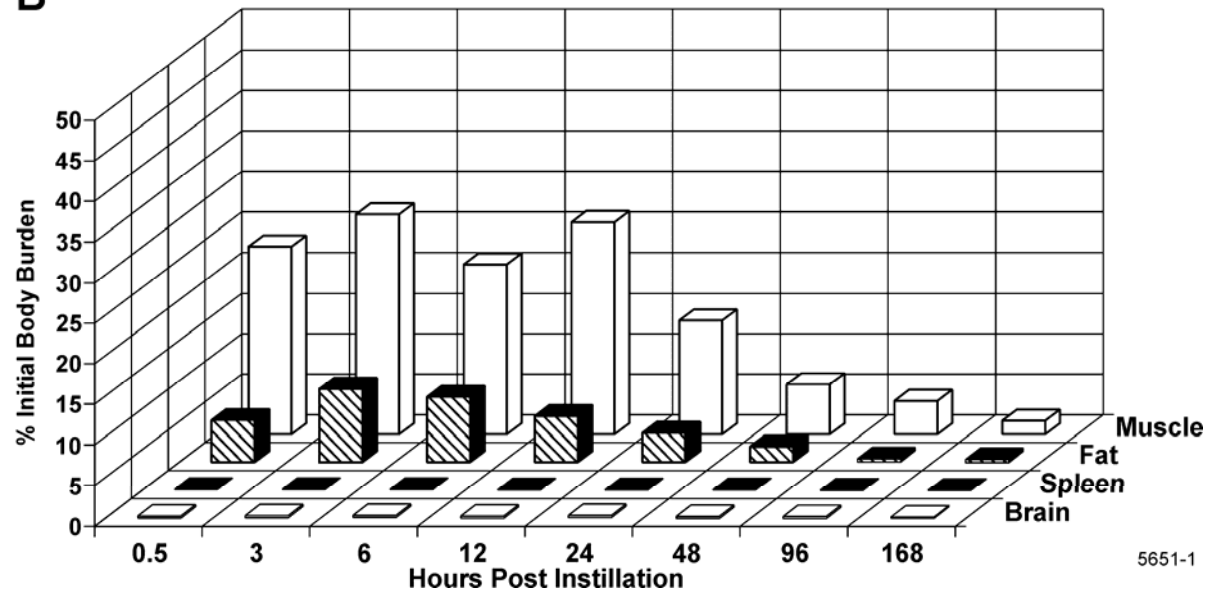
- **The major sources of brevetoxin exposure through ingestion of contaminated shellfish and by inhalation of sea spray during red tide events.**
- **Brevetoxin is absorbed rapidly into the blood and distributed widely throughout the body.**

Absorbed Brevetoxin Distributes Throughout the Body

A



B



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Background (Continued)

- **Toxic effects include:**
 - **Neurotoxicity**
 - **Bronchoconstriction in humans and in normal and “asthmatic” sheep**
 - **Alterations in the function of cells contributing to immune responses in sheep lung**
 - **Impairment of antibody mediated immune responses in rats**
 - **DNA damage in human lymphocytes in vitro**

Background (Concluded)

- **Placental transport of pollutants has been reported for several pollutants.**
- **This is relevant to fetal brevetoxin exposure because:**
 - **Developing nervous system a sensitive target.**
 - **Fetal immune system develops first within the liver and all maternal blood passes through the fetal liver before being distributed systemically.**
 - **Fetus more susceptible to genotoxins.**

Purpose

- **The purpose of this study was to examine the distribution of brevetoxin-3 administered to pregnant mice and determine the extent of placental transport to fetuses.**

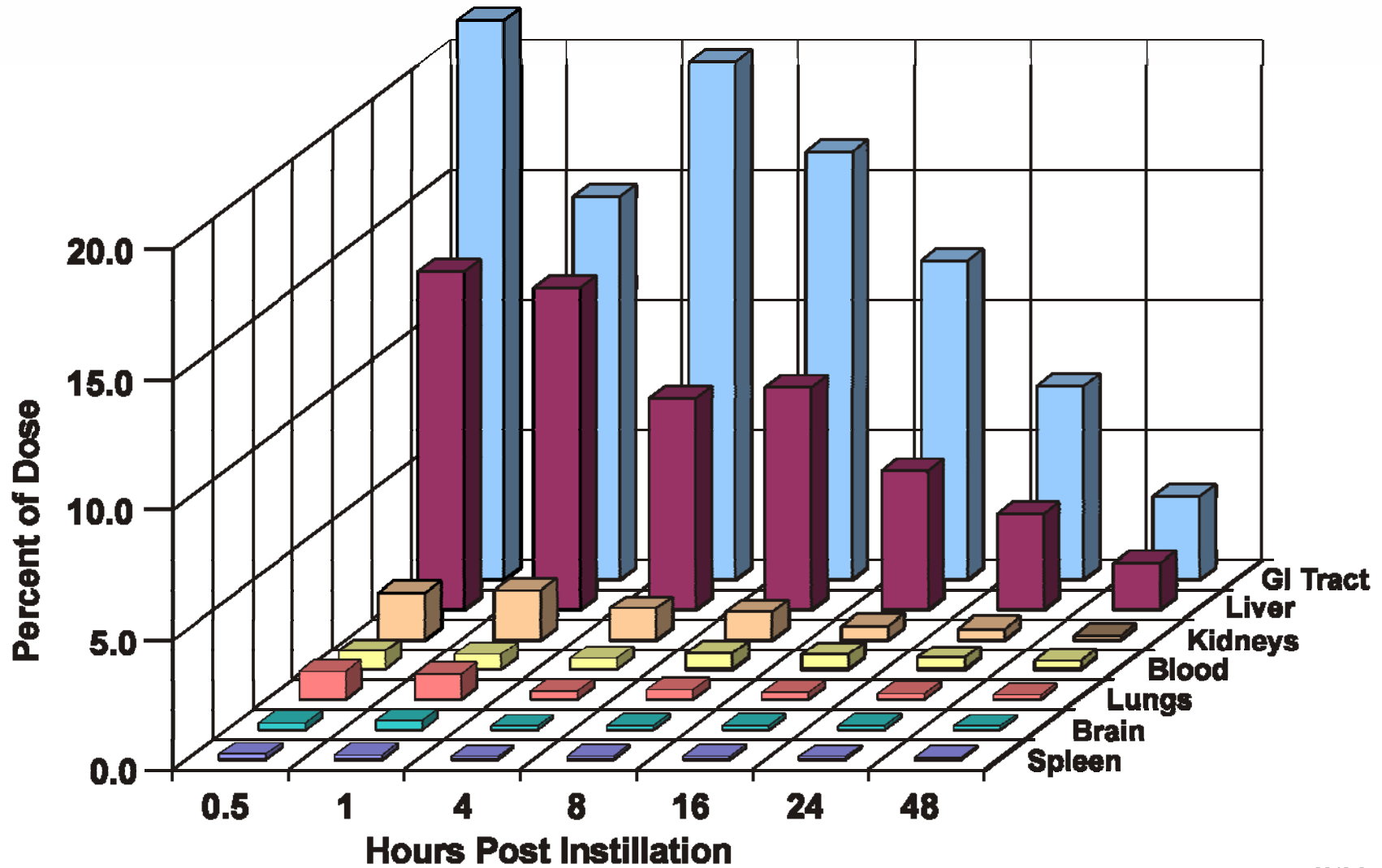
Methods

- **Intratracheal Instillation Study**
 - **Female CD-1 mice intratracheally instilled with ^3H -brevetoxin (1.3 μCi ; 0.14 $\mu\text{g}/\text{animal}$) once on day 15 -18 of gestation.**
 - **Groups of 4 or 5 were euthanized 0.5, 1, 4, 8, 16, 24 and 48 hours after dosing and tissues taken for radiochemical analysis.**
 - **Milk was obtained from the stomachs of one set of pups born before the 48 hr scheduled sacrifice.**

Methods (Concluded)

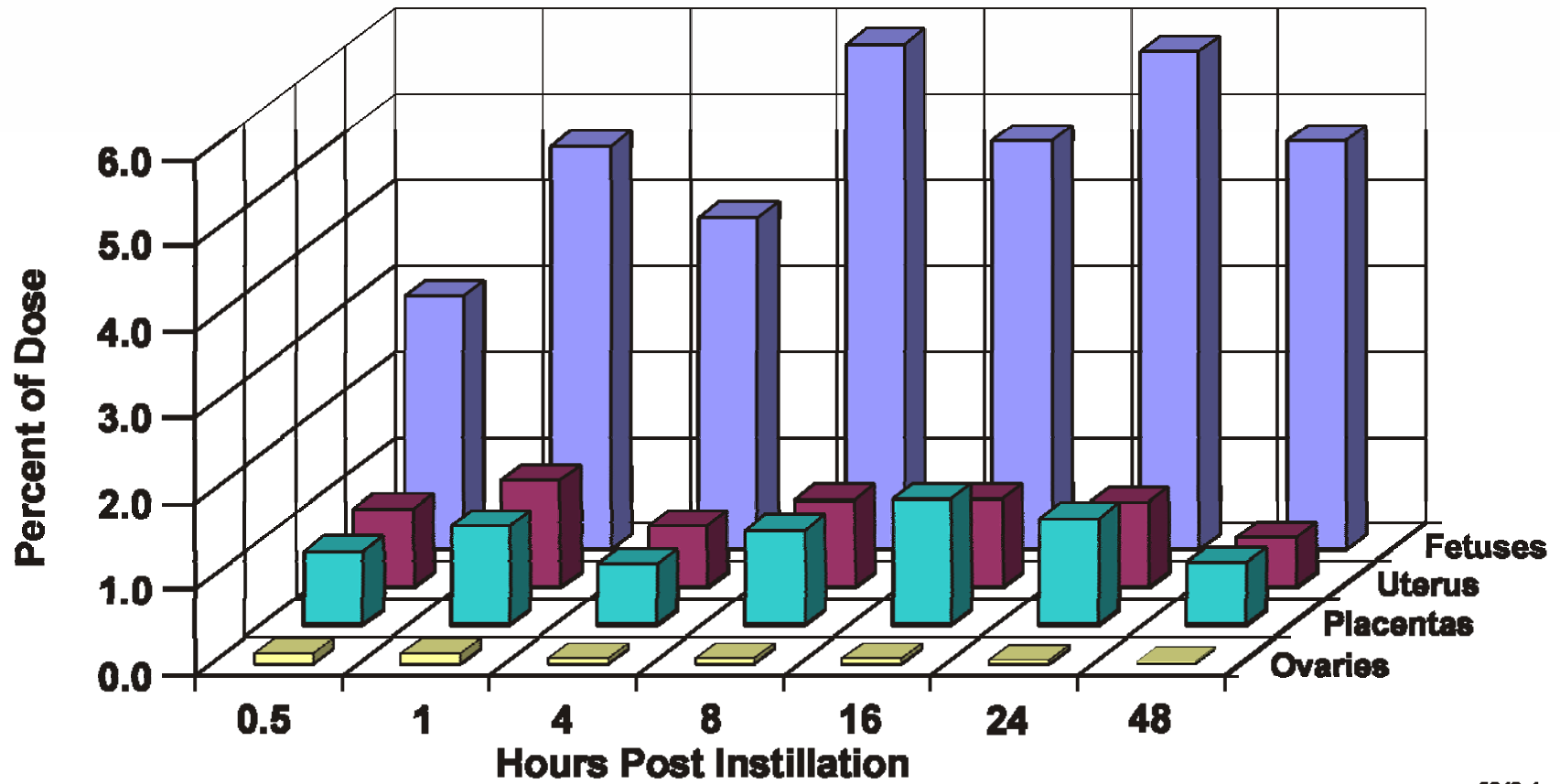
- **Exposure by osmotic minipump**
 - **Four pregnant mice were surgically implanted with a micro-osmotic minipump containing ^3H -brevetoxin (0.13 $\mu\text{Ci/day}$; 14 ng/day).**
 - **Mice were sacrificed 72 hours later and tissues collected.**

Results



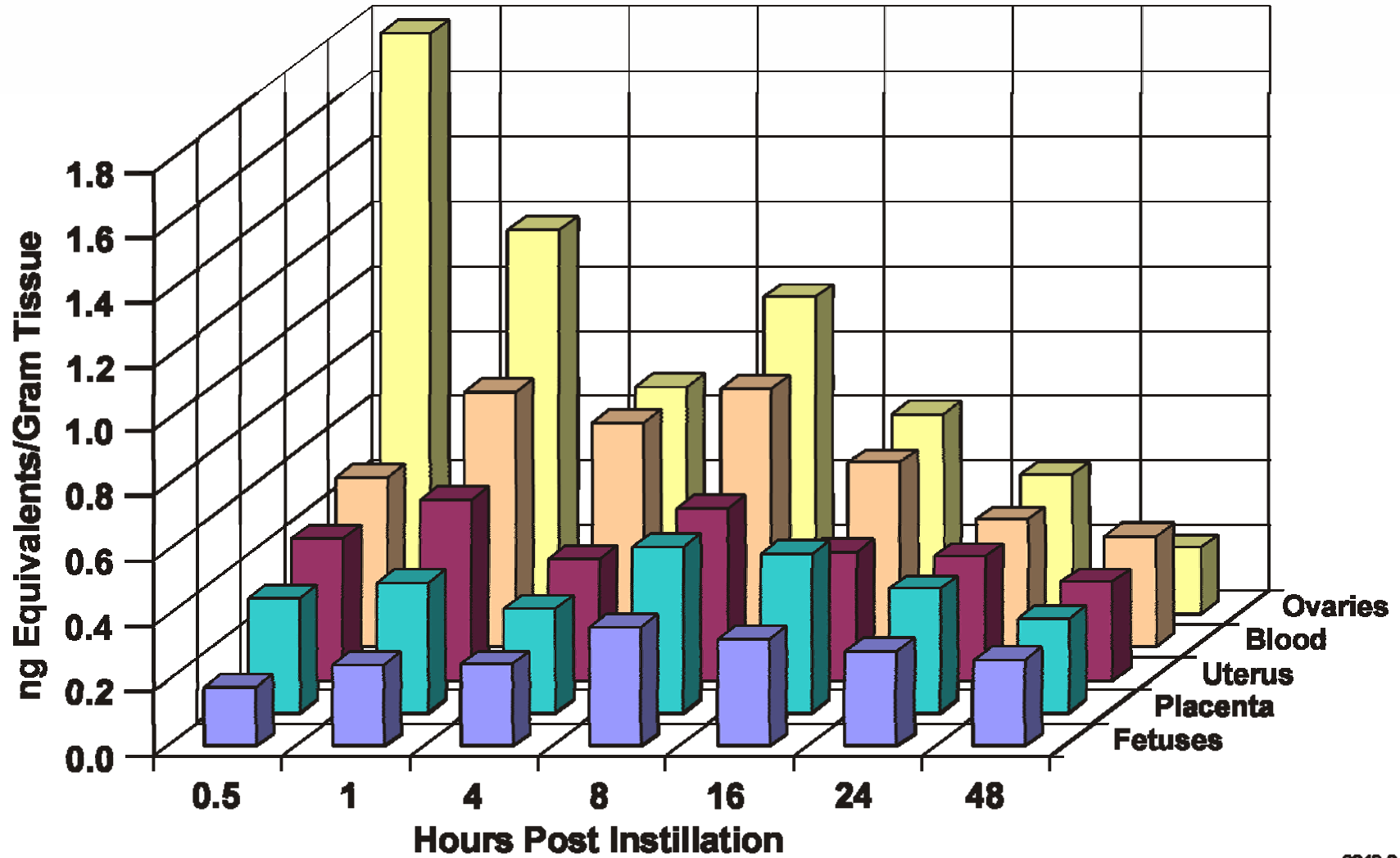
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Results



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Results

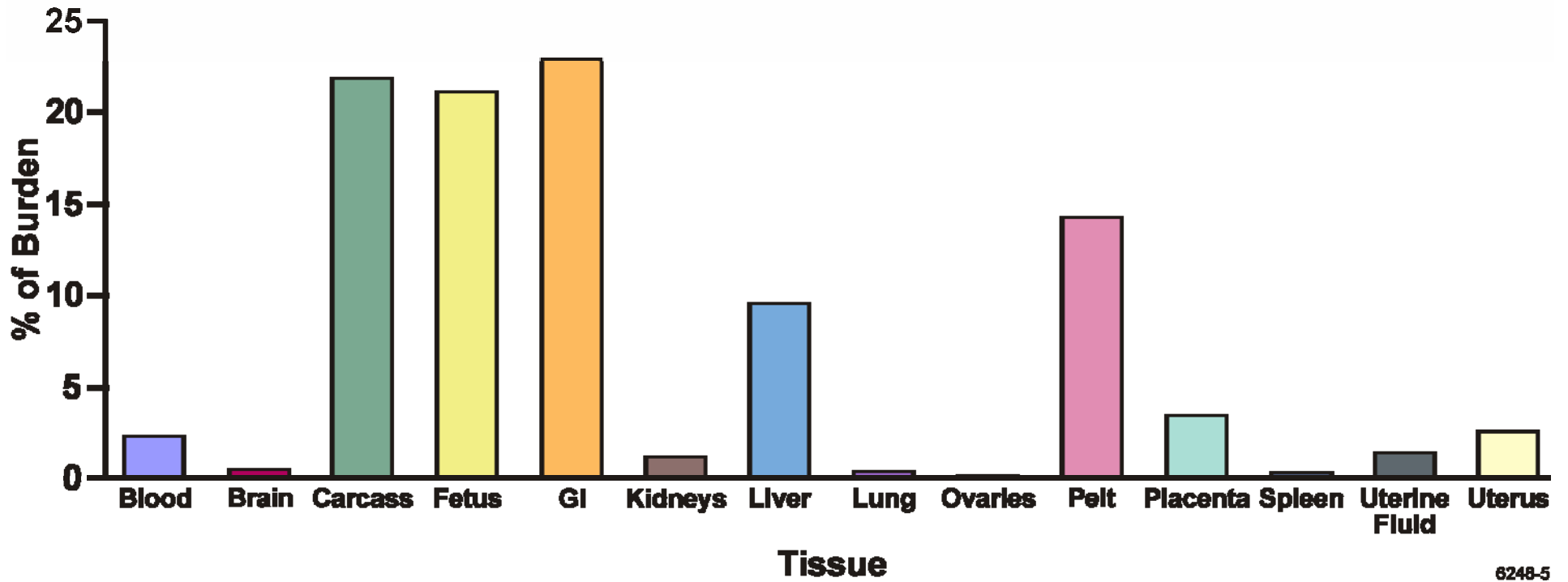


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Clearance Half-Times and Tissue Doses

Tissue	Half Time (hours)	Dose (ng/g-h)
Blood	39.2	23.3
Brain	1.7	13.4
Spleen	16.9	16.6
Ovaries	20.2	24.2
Uterus	71.4	18.2
Placenta	43.6	19.4
Fetuses	83.6	14.1

Results



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Concentrations in Selected Tissues

Tissue	Brevetoxin Equivalents ng/g
Blood	0.28 ± 0.23
Liver	0.36 ± 0.07
Spleen	0.14 ± 0.02
Ovaries	0.17 ± 0.02
Placenta	0.18 ± 0.01
Fetuses	0.10 ± 0.02

Summary

- **Brevetoxin equivalents distributed to uterus, placenta, fetus, and were ingested in milk, however we do not know whether the material was parent compound, metabolites, or both.**
- **Relative concentrations of brevetoxin equivalents were different following bolus versus continuous administration.**
- **Results of this study are currently in press in the journal Toxicon.**

Future Studies – Brevetoxin

- Hypothesis
 - *In utero* and perinatal exposure to brevetoxins will result in immunotoxicity in offspring of dams exposed by inhalation

Experimental Design Immunotoxicity in the Fetus and Offspring

- **Pregnant dams will be exposed by inhalation to brevetoxin-3 by inhalation from gestational day 5 to term.**
- **Effects on immune function will be examined in the dams, fetuses, juveniles, and young adult rats born and reared by the brevetoxin exposed dams.**
- **Endpoints:**
 - **Flow cytometric analysis of lymphocyte populations in thymus and spleen of fetal and maternal tissue**
 - **Lymphocyte proliferation in response to mitogen challenge in vitro (T cell function)**
 - **Primary antibody response**
 - **Histopathology**

Experimental Design

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Proposed New Studies – Microcystin Placental Transport

- **Microcystins are demonstrated hepatotoxins, tumor promoters, and may be genotoxic.**
- **A product of cyanobacteria, they occur globally in surface waters.**
- **Conflicting data on the effects of microcystin on the developing fetus have been reported.**

Microcystin Placental Transport

- **The purpose of the study proposed to the Florida Department of Health is to:**
 - **Quantitate fetal uptake of microcystin in fetal tissue following repeated exposure of pregnant dams**
 - **Relate fetal dose to maternal dose**

Acknowledgements

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