

The Safety of AQUI-S®

(an experimental fish anesthetic)

to Rainbow Trout



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U.S. Fish and Wildlife Service

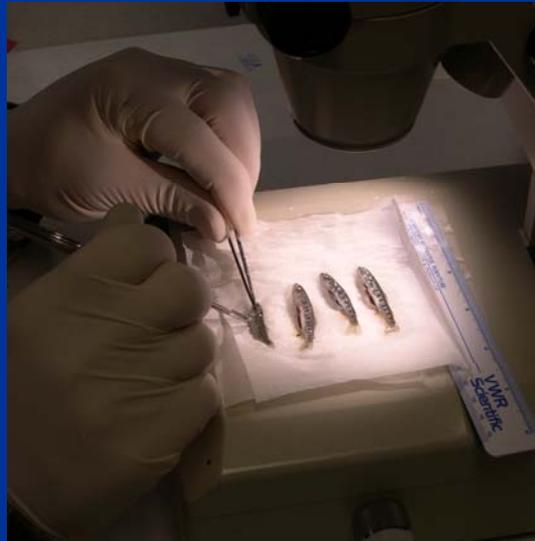
Aquatic Animal Drug Approval Partnership Program

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Today's Presentation

- ◆ AQUI-S and the FDA approval process
- ◆ AQUI-S Target Animal Safety Study (2005)
- ◆ Use AQUI-S via AADAP



- Fish anesthetic developed by AQUIS New Zealand, Ltd.
- Synthetic
 - (54% isoeugenol)
- Approved in New Zealand, Australia, & Chile for use on food fish (no withdrawal period required)
- Candidate for FDA approval as “zero-withdrawal” anesthetic





CENTER FOR VETERINARY MEDICINE

- ◆ Product chemistry (AQUIS, NZ)
- ◆ Human Safety (AQUIS, NZ + USGS)
- ◆ Environmental Safety (AQUIS, NZ + USGS)
- ◆ Efficacy (AADAP)
- ◆ Target Animal Safety (AADAP)

New Zealand Label

AQUI-S[®]

Aquatic Anaesthetic

**for use in the handling and harvesting
of fish and other seafood**

ACTIVE INGREDIENT : 540 g/L isoeugenol

Currently “Proposed” U.S. Label Claim

- Part 1: Use AQUI-S at 20 – 40 mg/L to sedate all freshwater salmonid fishes for management and handling purposes.
- Part 2: No withholding period required; treated fish may be assimilated into the food chain at any time.



AQUI-S Target Animal Safety Study March 2005

- ◆ Introduction
- ◆ Design & Conduct
- ◆ Results/Discussion
- ◆ Conclusions

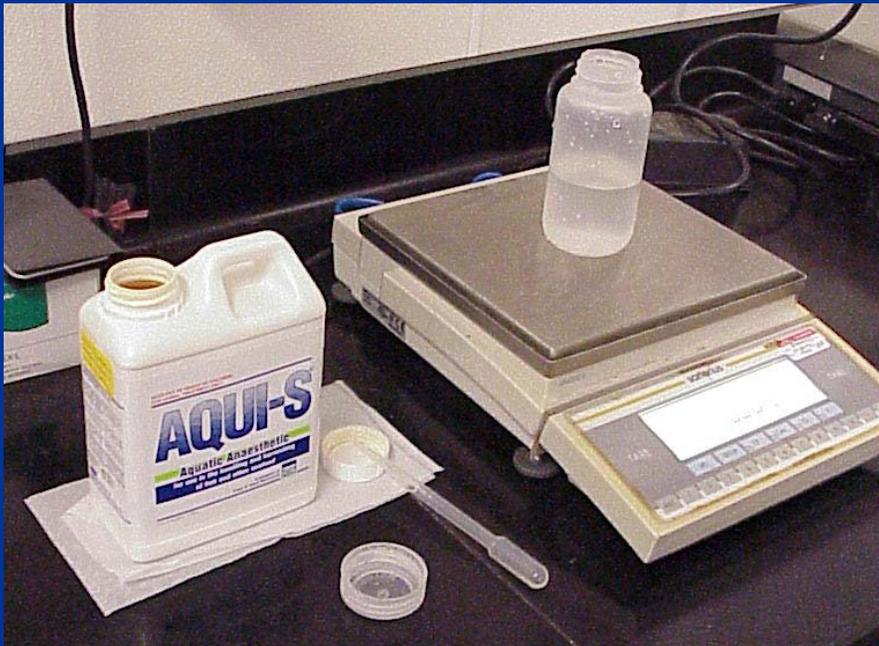


Introduction

- ◆ All TAS studies ... "margin of safety."
- ◆ TAS studies with therapeutic drugs...
 - ◆ Margin of safety = concentration (e.g., 3x, 5x, or 10x higher than highest efficacious concentration listed on the product label)
- ◆ TAS study with AQUI-S....
 - ◆ Margin of safety = duration of exposure at a given concentration (e.g., Y minutes at X mg/L).

Objective

- ◆ For 20, 40, and 80 mg/L, determine longest exposure durations (minutes) at which survival was $> 95\%$.



Test Article and Test Species

◆ AQUI-S

◆ 0, 20, 40, 80 mg/L

◆ Rainbow trout

◆ 1.5 inches

◆ $H_2O = 15^{\circ}C$

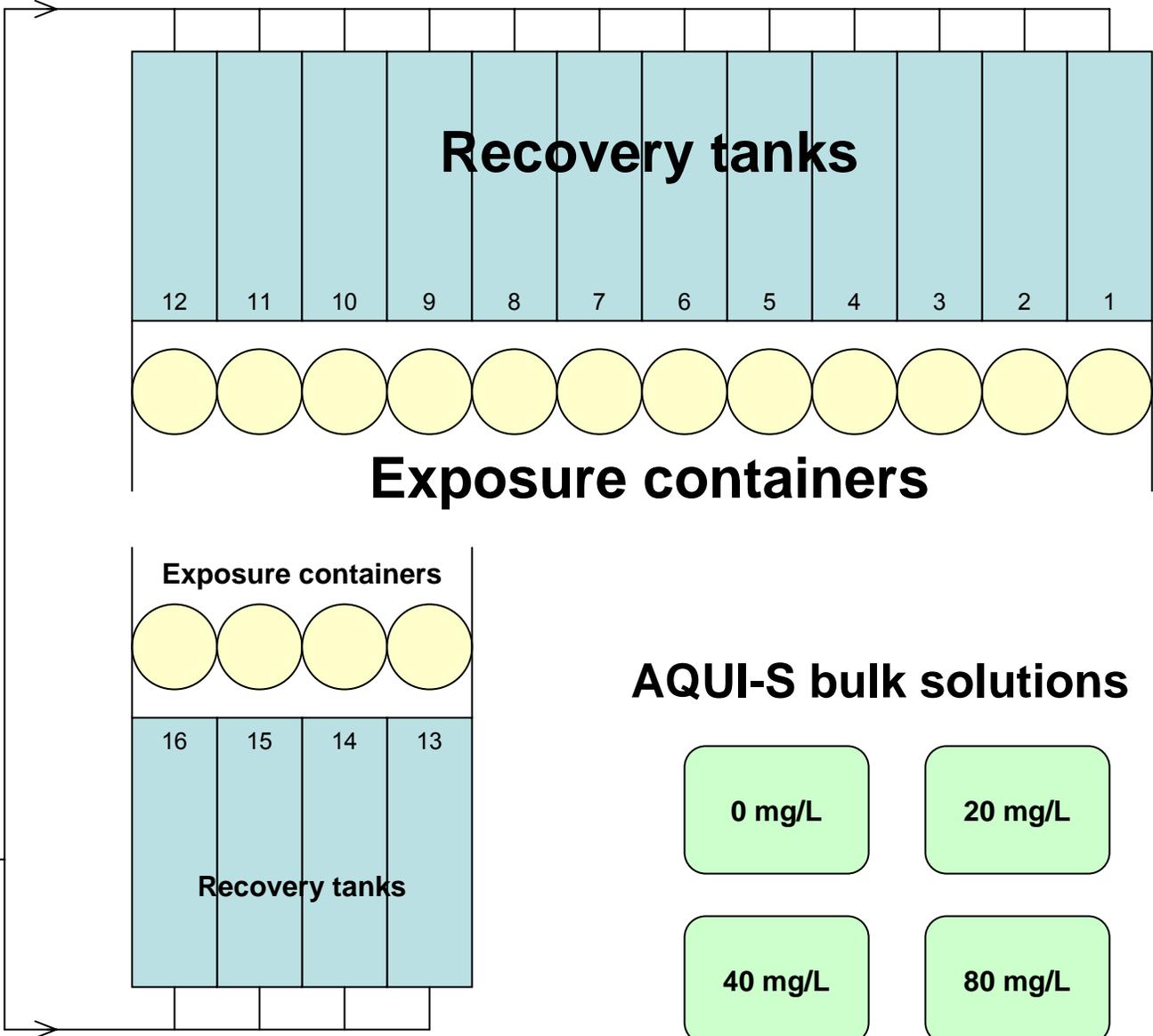


Study Design

Exposure duration (minutes)	Exposure concentration (mg/L)			
	0	20	40	80
T1	22.1	22.1	5.5	1.9
T2	35.0	35.0	6.3	2.1
T3	51.5	51.5	9.0	2.7
T4	66.2	66.2	13.0	3.0

- Exposed four groups of test fish (n = 20 fish per group) at each of the 16 exposure regimens (concentration x duration).
- One "exposure/recovery replicate" = (exposure event) + (24-h recovery period)

**One exposure/
recovery
replicate
(24+ hours)**



Study Conduct

- Study protocol (FDA approved)
- Good Lab Practices (QA inspection)
- Blinding
- Randomization
- Dose verification



Exposure and Recovery

Start exposure



Expose for T1, T2, T3, or T4



Start 24-h recovery



End 24-h recovery



Water Quality



Dose Verification



Exposure Data

Behavior



Recovery Data

Survival & Behavior



Water Quality



Histology Samples



Results

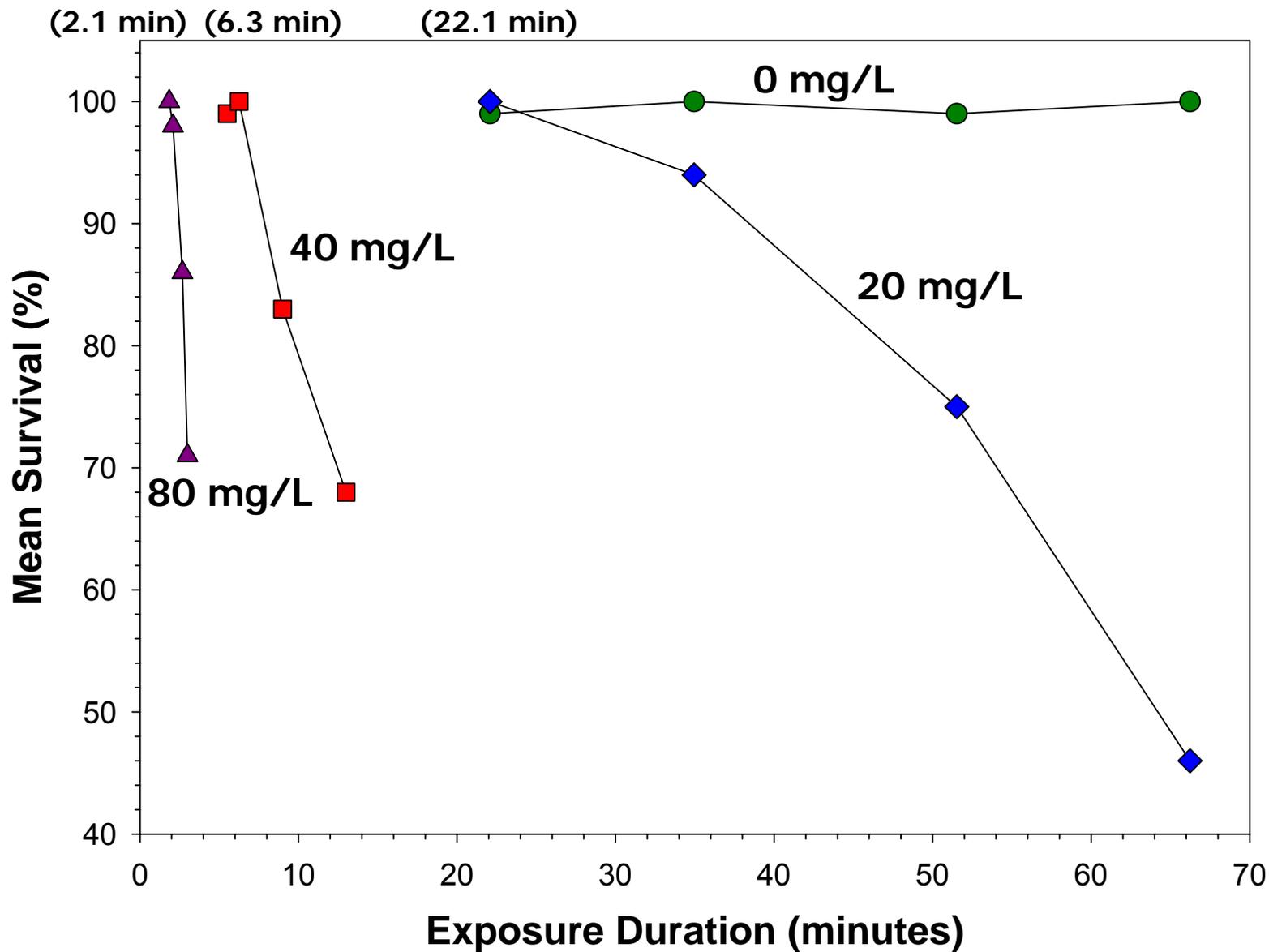
Water Quality	Temp (C)	DO (mg/L)	pH
Exposure	15.0	7.5	7.9
Recovery	15.5	7.4	7.8

Dose Verification	Measured AQUI-S concentrations (mg/L)		
Mean	22	42	83
% Difference	+10	+5	+4

Results - Behavior

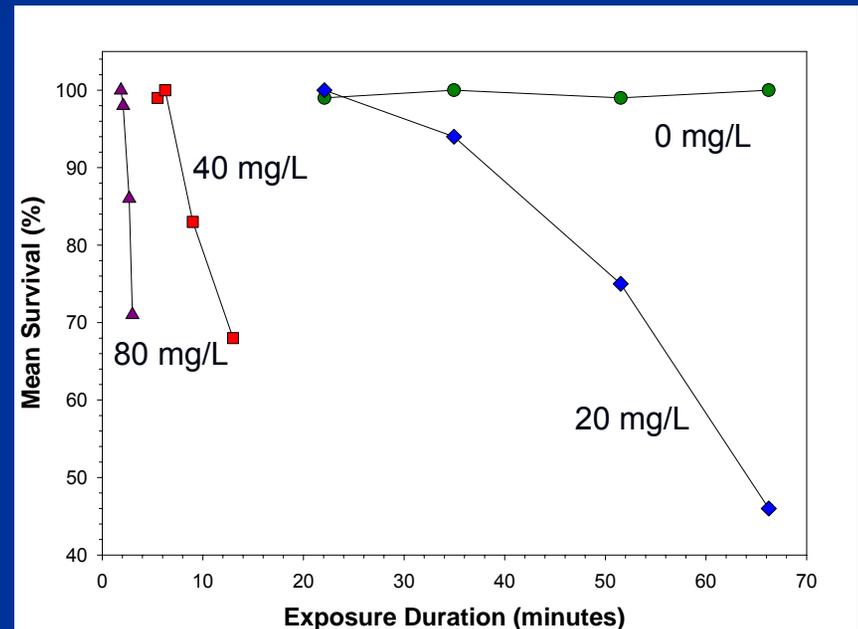
- Exposure Behavior (20, 40, and 80 mg/L)
 - Temporary “headshaking” in some fish tested at 40 or 80 mg/L (lasts only a few seconds; does not appear related to survival).
 - Loss of reactivity and equilibrium; slowed opercular movement (some fish w/no opercular movement).
- Recovery Behavior
 - “Normal” for those fish that survived.

Results – Survival (mean %)



Preliminary Conclusion 1

- Exposure concentration and exposure duration both affect behavior and survival.
- Note: Exposure duration appears to become “relatively more important” to survival as exposure concentration increases.



Preliminary Conclusion 2

■ Estimated exposure duration “margins of safety”*

AQUI-S concentration (mg/L)	Exposure duration (minutes)
20	22
40	6
80	2

*observed survival \geq 98%

Finally

- We still need to evaluate the histopathology data to...
 - conclude if the results of this study support the approval of AQUI-S for use at 20 – 40 mg/L to “sedate all freshwater salmonids for management and handling purposes.”

More AQUI-S® Information

- ◆ AQUI-S use via AADAP
 - ◆ 406-994-9904 (Dave Erdahl)
 - ◆ 406-994-9905 (Bonnie Johnson)
 - ◆ www.fws.gov/fisheries/aadap



- ◆ AQUIS New Zealand, Ltd.

- ◆ www.aqui-s.com

