Aquatic Animal Drug Approval
Partnership Program
(AADAP)

Potential Zero-Withdrawal Anesthetics for Use in Fisheries and Aquaculture

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Need for Finfish Anesthetic

- Minimize stress during capture and handling of fish
  - Vaccination, marking, grading, spawning, transport, etc.
- Minimize adverse physiological and behavior effects
- Minimize suppression of immunological capacity (by minimizing stress-related cortisol release)
- Improve product quality
- No withdrawal period required

Ideal Anesthetic

- Availability
- Cost-effectiveness
- Ease of use
- Nature of use
- Safety for the user
- Non-toxic to fish
- No persistent effects
- Sedate fish < 3 min
- Fish recover in < 5 min

- Potential for FDA approval
- Mammalian toxicology
- Persistent residues
- Withdrawal period
- Margin of safety

Compounds used to sedate fish

- Heavy alcohols
- Ether
- Chlorether
- Brominated alcohols
- Barbiturates
- Chloral hydrate
- Urethane
- Metomidate
- Phenoxyethanol
- Quinaldine sulfate
- Tricaine methanesulfonate
- Chlorbutanol
- Benzocaine
- Clove Oil
- AQUI-S®
- CO_2 gas
- Etomidate

Whittled down list

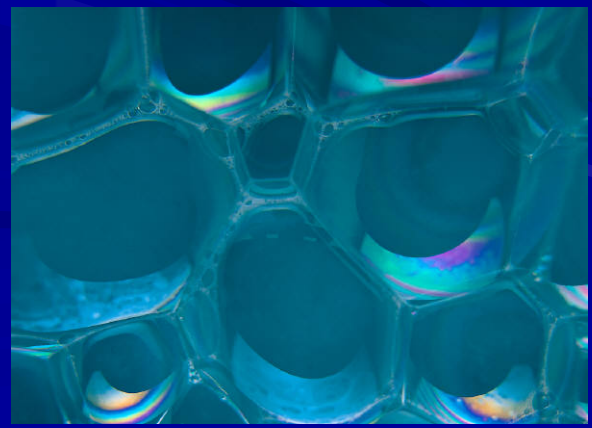
- Unwanted systemic side effects
- Limited safety margins
- Potential for zero-withdrawal
  - CO_2
  - Metomidate
  - Benzocaine
  - Tricaine Methanesulfonate
  - Clove Oil
  - AQUI-S®

Components of a U.S. Drug Approval

- Demonstrate the drug is
  - effective
  - safe to the environment, humans, and fish
  - can be manufactured (pure) consistently.
- U.S. drug sponsor (privately owned company) willing to apply for New Animal Drug Application approval

CO_2

- Gas and Sodium bicarbonate (142 – 642 mg/L for 5 minutes)
- Unapproved New Animal Drug of Low Regulatory Priority
- Effective anesthetic….results inconsistent
- No sponsor willing to pursue an NADA
- No withdrawal period
- Extremely stressful to fish



Metomidate

- Trade name – Aquacalm®
- Sponsor – Syndel International Inc., Vancouver, BC, Canada
- Used for sedation or anesthesia of fish
  - Sedate: 0.1 – 1.0 ppm; anesthetize: 5 – 10 ppm
- Suppresses cortisol stress response (Iverson et al. 2003; Small 2003)
- Not for use in fish intended for human consumption
- Available in the U.S. under an INAD for ornamental fish only (sponsor pursuing FDA approval for ornamental fish)

Benzocaine

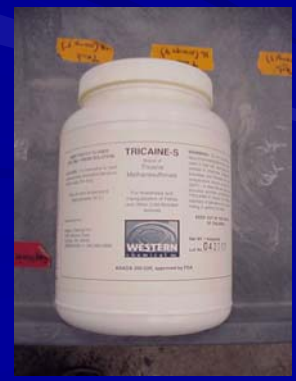
- Spray used in the mouth and throat; short-acting local anesthetic; interferes with the ability of certain nerves to conduct electrical signals
- Identified as an AFWA priority drug; application initially encouraged by FDA
- MultiState Grant funding available
- USGS UMESC poised to continue testing
- Human food safety – required two 90-d feeding studies

More on Benzocaine

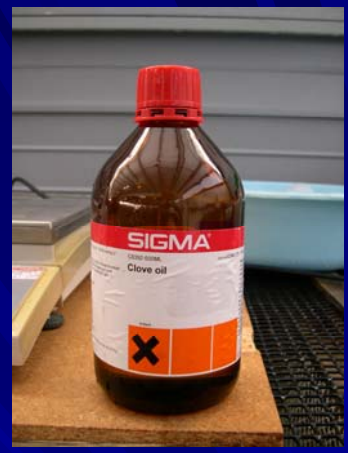
- No sponsor willing to pursue an NADA
- Formulation needed tweaking – increase water solubility
- Preliminary residue depletion studies indicated no assurance of zero-withdrawal
- Alternate anesthetic surfaced (1995)
- Limited suppression of cortisol stress response (Iverson et al. 2003)

Tricaine Methanesulfonate

- Tricaine-S® - Western Chemical; Finquel® - Argent Chemical Laboratories
- Approved "back in the day" for Ictaluridae, Salmonidae, Esocidae, and Percidae; approval based primarily on peer-reviewed literature
- Very effective anesthetic; 21- day withdrawal period
- Sponsors not willing to invest $$ to conduct studies required to reduce withdrawal period
- Current CVM definition of "adequate margin of safety" would likely reduce the dose range
- Limited suppression of cortisol stress response (Iverson et al. 2003)



Clove Oil



- Used throughout the world – food flavoring; used in dentistry
- Effective anesthetic; suppressed cortisol stress response (Small 2003)
- Clove oil is a “crude” product – not made consistently from batch to batch, or by different manufacturers
- 85 – 95% eugenol, 5 – 15% isoeugenol and methyleugenol

More on Clove Oil

- FDA Guidance for Industry #150 – Status of Clove Oil and Eugenol for Anesthesia of Fish – unapproved drug
  - Eugenol – GRAS in animal feed (21 CFR 582.60) – an equivocal carcinogen
  - Methyleugenol – carcinogenic to rodents
  - Clove oil - considered GRAS – added directly to human food (21 CFR 184.1257)
  - Isoeugenol – cleared for use in human food (21 CFR 172.515) – toxicity not known
- Presence of methyleugenol in clove oil raised the level of concern for human safety
- No sponsor willing to pursue an NADA

AQUI-S®

- 50% isoeugenol
- Approved in numerous countries as a zero-withdrawal anesthetic
- Effective anesthetic for “rested harvest”
- Sponsor – AQUI-S New Zealand, Ltd (developed by New Zealand Institute for Crop and Food Research)
- Supported by AFWA (Drug Approval Working Group) as potential zero-withdrawal
- Isoeugenol being tested by the National Toxicology Program

More on AQUI-S®

- Sponsor and partners working towards completing drug approval data requirements
- An effective anesthetic to sedate all freshwater finfish
- Adequate margin of safety above highest proposed concentrations
- Suppressed cortisol stress response (Iverson et al. 2003)
- Currently, best chance of gaining FDA-approval as a potential zero-withdrawal anesthetic for finfish

Summary

- U.S. aquaculture and fisheries management need a zero-withdrawal anesthetic
- Many compounds have been evaluated
- Several anesthetics are proven to be effective and show promise
- AQUI-S® is the “best” candidate
- ANZL is an “engaged” sponsor and is working towards NADA approvals in the U.S.

??Questions??