DOI Mission

- Protects and manages the Nation’s natural resources & cultural heritage

- Provides scientific & other information about those resources

- Honors trust responsibilities & commitments to American Indians, Alaska Natives & affiliated island communities
Some Toxicological Research
Very limited regulatory authority on chemicals

- U.S. Geological Survey
- U.S. Fish and Wildlife Service

1. Toxicological research (hypothesis testing)
2. Environmental contaminant biomonitoring
3. Natural Resource Damage Assessment
4. Registration of “shot” used in hunting
5. Registration of chemicals used in aquaculture

Embrace 3 R’s
Registration of Non-toxic Shot

lead replacements:
- steel
- bismuth-tin
- copper-clad iron
- tungsten-bronze
- tungsten-iron
- tungsten-matrix
- tungsten-nickel-iron
- tungsten-polymer
- tungsten-tin-bismuth
- tungsten-tin-iron
- tungsten-tin-iron-nickel

Bottom Line – many shot types registered using existing information, risk assessment and no toxicity test (harmonized with Canada)
Screening and Testing Candidate Fishery Management Chemicals

- Toxicants and therapeutics

- Developing a tiered approach:
  - Physiochemical data to identify SAR
  - Developing *in vitro* fish cell lines to replace *in vivo* testing
  - Genomic analyses attempting to identify biomarkers of toxicant-sensitive and resistant species
Adverse Outcome Pathway

Toxicant: First- and second-generation anticoagulant rodenticides
- Irreversible inhibition of vitamin K by binding at Tyr 139
- Limited formation of vitamin K hydroquinone
- Failure to carboxylate clotting factors

Macromolecular Interaction: Antidote vitamin K
- + clotting time (PT, RVVT)
- Ischemia, cell necrosis
- Bone density, anti-inflammatory, cell proliferation

Cellular Response: Clearing of carboxylated clotting factors II, VII, IX, X
- Hemorrhage
- Skin, Muscle, Renal, GI, CNS
- Reproductive, Respiratory

Multiple Organ Response: Organ dysfunction
- Acidosis
- Hypervolemic shock
- + Susceptibility to disease

Organism Response: Anemia
- Mortality
- + Fitness
- Body condition

Population Response: Little consequence for abundant species
- Moderate to serious consequence for species of special conservation status

Key:
- Established Linkage
- Plausible Linkage
- Diagnostic Tool to verify death related to rodenticides
- Hypothetical Linkage

Extrinsic and Intrinsic Pathways:
- Thromboplastin, Tissue Factor
- FVII, Vit K Dependent
- FIX, Vit K Dependent
- FX, Vit K Dependent
- FXa, FV, PL, Ca²⁺
- Prothrombinase Complex
- Thrombin
- Fibrin
- Fibrinogen

Vitamin K Cycle:
- Vitamin K Epoxidation
- Vitamin K Hydroquinone
- Vitamin K Quinone