

ANIMAL METRICS:
TRACKING NEW
APPROACH METHOD
(NAM) IMPACTS ON
ANIMAL USE

SACATM MEETING
21 SEPTEMBER 2022
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AGENDA

§ GOAL OF ANIMAL USE METRICS

§ DEFINITIONS

§ TRACKING NAM IMPACT

§ ANIMAL USE PROGRAM ELEMENTS

§ DOW'S APPROACH TO ASSESS NAM IMPACTS ON ANIMAL USE

§ CONCLUSION

PUBLICATION ON ANIMAL METRICS

Concept Article

ALTEX 39(1), 2022

Animal Metrics: Tracking Contributions of New Approach Methods to Reduced Animal Use

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Goal: Determine how NAMs are contributing to reduced animal use

Dow's Approach:

- All NAM data provides useful information with some value for animal savings
- Approach may be improved or adapted for other organizations

DEFINITIONS

§ [NEW APPROACH METHODS \(NAMs\)](#) – NON-ANIMAL APPROACHES FOR TESTING AND ASSESSMENT (E.G., COMPUTER-BASED MODELING, READ-ACROSS, *IN CHEMICO* OR *IN VITRO* METHODS)

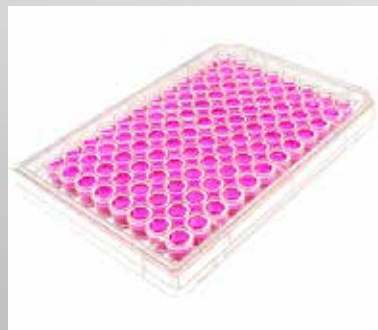
§ [ANIMAL](#) – “ANY VERTEBRATE ANIMAL PRODUCED OR USED IN RESEARCH, TEACHING OR TESTING” (AALAS)

§ INCLUDES OFFSPRING BORN DURING STUDIES

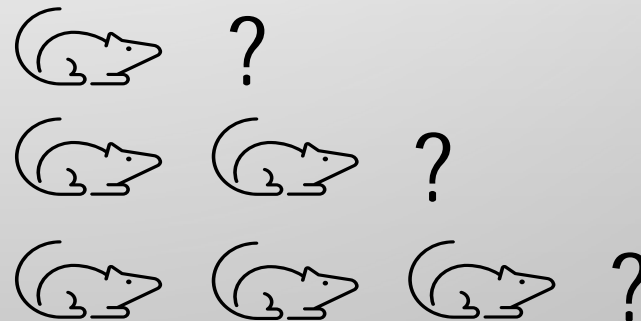
§ DOES NOT INCLUDE FETUSES, EMBRYOS OR OTHER VERTEBRATES PRIOR TO HATCHING

§ EXCLUDES ANIMALS MONITORED IN FIELD STUDIES

§ [EQUIVALENT ANIMAL SAVINGS](#) – THE ESTIMATED NUMBER OF ANIMALS THAT WOULD BE USED TO GENERATE EQUIVALENT INFORMATION TO WHAT IS PROVIDED BY A NAM

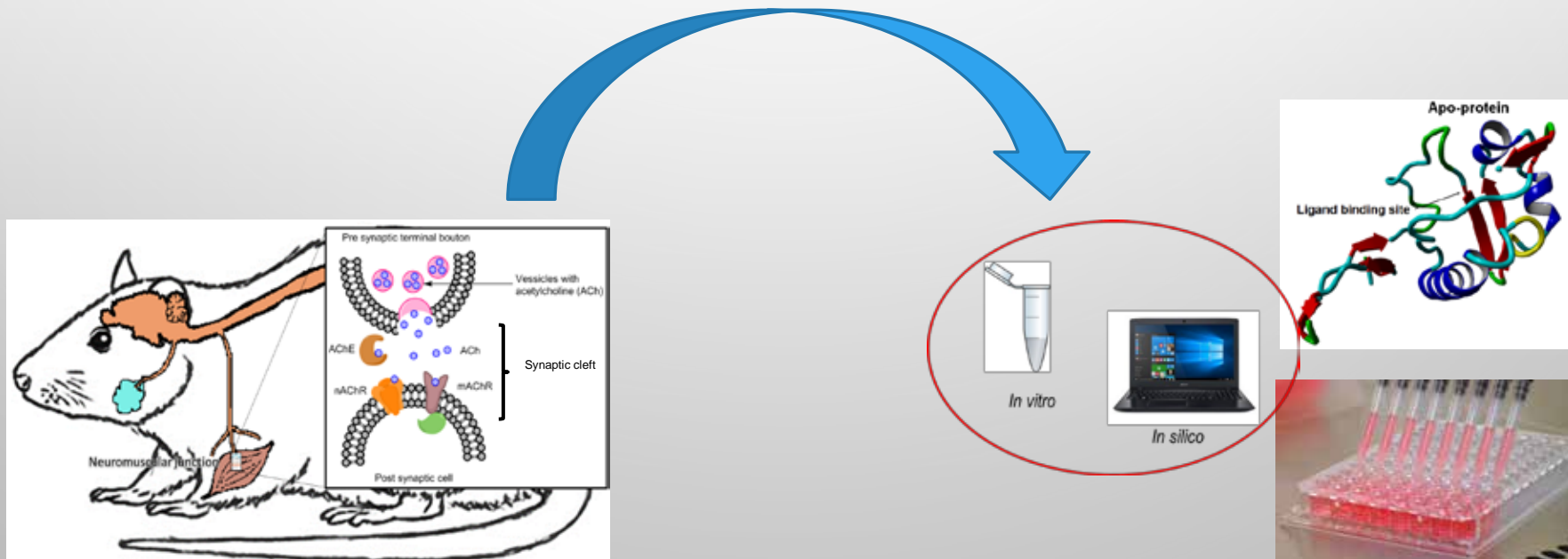


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WHY TRACK NAMS IMPACT ON ANIMAL USE?

- § IMPACT OF NAMS ON ANIMAL USE NUMBERS OVER TIME
- § MONITOR THE UPTAKE OF NAMS OVER TIME
- § ACCOUNTABILITY FOR RESOURCES SPENT ON NAM DEVELOPMENT
- § IDENTIFICATION OF AREAS WHERE NAM DEVELOPMENT IS STILL NEEDED



ANIMAL USE PROGRAM ELEMENTS

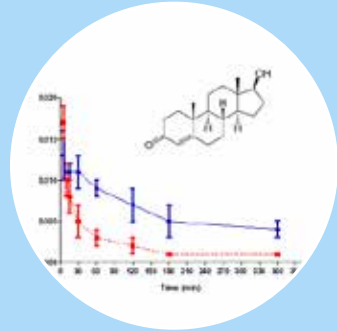
- § DEFINE BASELINE ANIMAL USE (DEFINED RULES FOR INCLUSION/EXCLUSION OF ANIMALS TO ENSURE CONSISTENCY IN FUTURE ASSESSMENTS)
 - § ANIMALS USED IN HOUSE OR AT CROs, INCLUDING CONSORTIUM-SPONSORED STUDIES
 - § MAMMALIAN AND NON-MAMMALIAN ANIMALS TRACKED SEPARATELY
 - § ECOTOX STUDIES USE LARGE NUMBERS OF ANIMALS
 - § STUDY TYPES: UNDERSTAND HOW STUDY REQUIREMENTS SHIFT FROM YEAR-TO-YEAR
 - § MULTI-YEAR AVERAGE OF ANIMAL USE (VARIABILITY DUE TO REGULATORY PROGRAMS, BUSINESS, ETC.)

ANIMAL SAVINGS DEPENDS ON NAM DATA USE



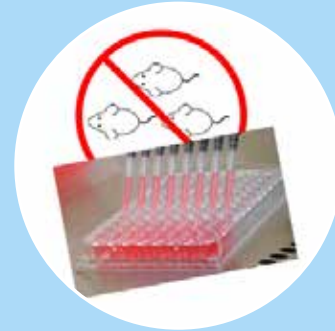
Early Screening/ Internal Decision Making

- Screening new chemistries
- Analog selection
- Decreasing animals needed for probe studies (targeted)
- RSSDS/MSDS (early development)



Supporting Data in a Regulatory Submission or Safety Assessment

- NAM results consistent with hazard data
- Data Use and Level of Uncertainty with available in vivo data
- NAM data on MOA; used in WOE
- NAMs used for EU cosmetics (animal use not permitted, but no formal testing requirements)



Full Substitute for an Animal Study in a Regulatory Submission

- NAMs accepted in place of required regulatory study (e.g., in vitro dermal sensitization)
- Waiving argument accepted (animal study no longer required)

- ANIMAL SAVINGS DEPENDS ON:
 - § HOW DATA ARE USED (I.E., WHAT DECISIONS ARE BEING MADE)
 - § LEVEL OF UNCERTAINTY
 - § EVEN WITHOUT REGULATORY ACCEPTANCE, DATA HAVE VALUE FOR INTERNAL DECISION-MAKING
 - § *IN SILICO* COMPUTATIONAL MODELS FOR BIOACTIVITY IDENTIFICATION (E.G., CANDIDATE SELECTION)
 - § STUDY WAIVING BASED ON AVAILABLE INFORMATION (E.G., READ-ACROSS, EXPOSURE-BASED WAIVING)

DOW'S APPROACH TO NAM IMPACTS ON ANIMAL USE

DOW'S TABLES WITH ANIMAL SAVINGS USING NAMS

§ *IN SILICO* HUMAN HEALTH AND ENVIRONMENTAL HAZARDS

§ *IN VITRO* ASSESSMENTS

§ "INTELLIGENT DESIGNS"

§ TOXICOKINETICS (*IN SILICO* AND *IN VITRO*)

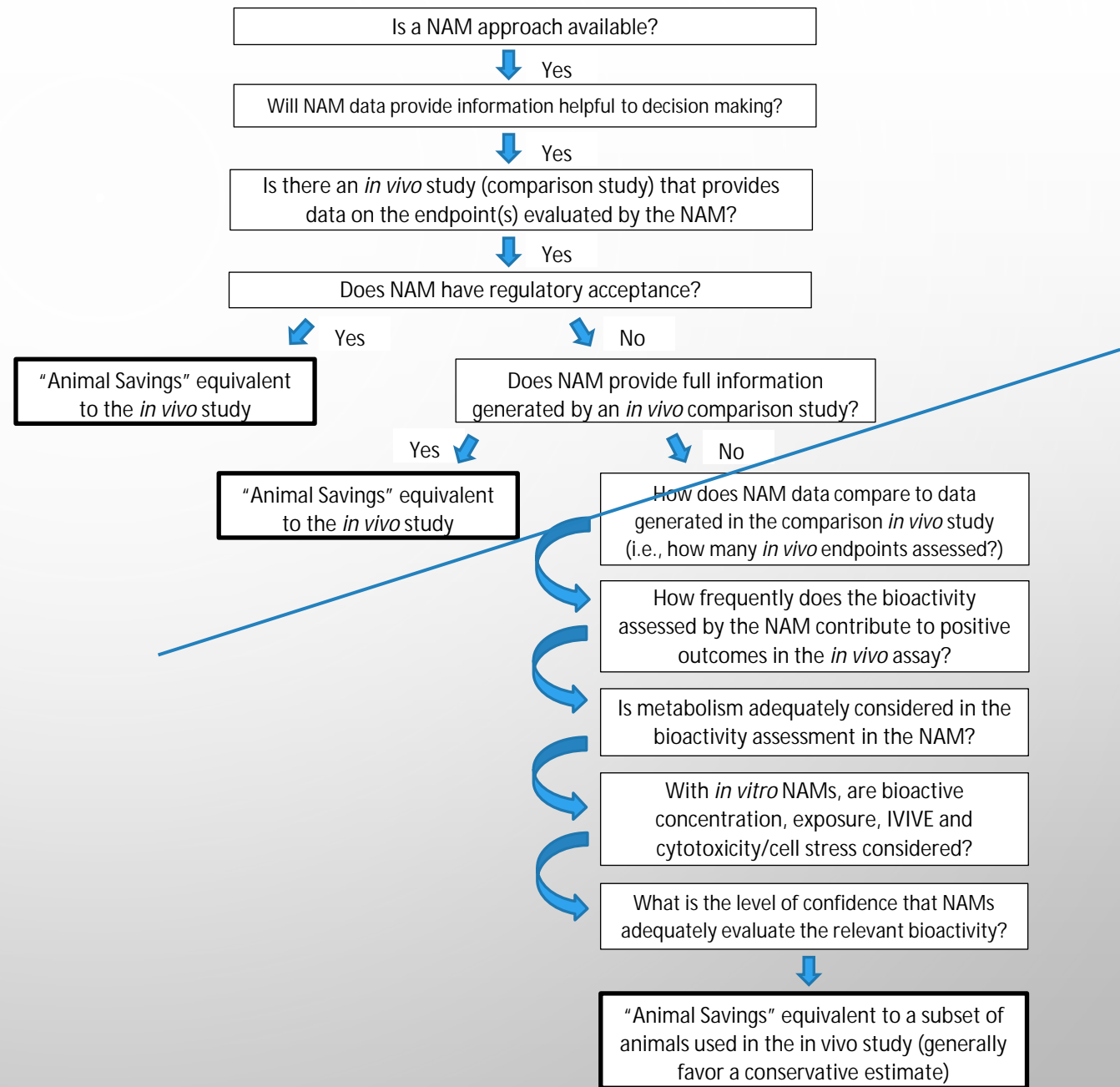
§ STUDY WAIVING

Tab. 4: Animal use reductions due to *in silico/in vitro* metabolism or bioaccumulation

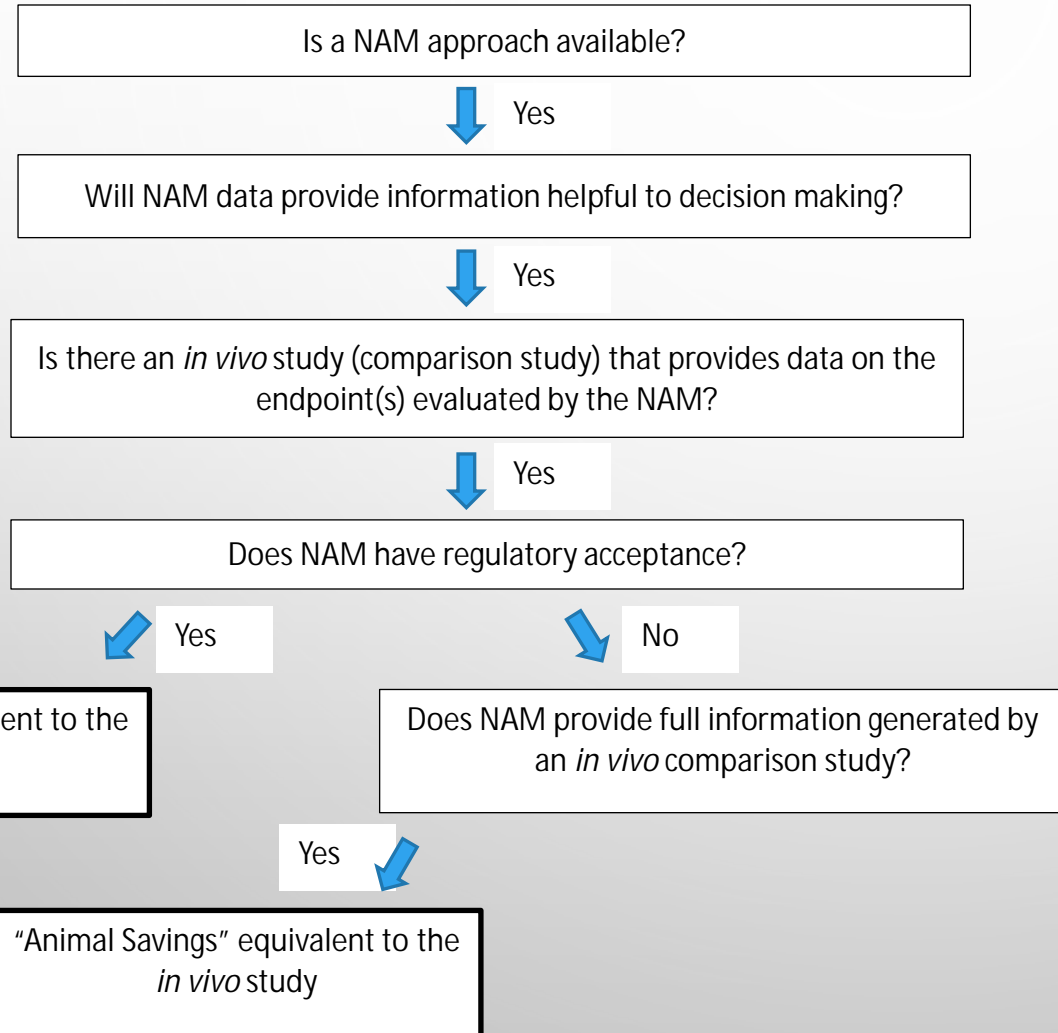
Endpoint addressed by NAM	Corresponding <i>in vivo</i> test	No. of animals <i>in vivo</i>	Animal savings using NAM	Rationale for percentage selected	No. of animals saved by NAM use
<i>In vitro</i> comparative metabolism (IVCM) (mouse, rat, rabbit, dog, human)	OECD ^a 417: <u>Toxicokinetics</u> (absorption, distribution, metabolism, and elimination; <u>ADME</u>) ^b with inclusion of multiple species for cross-species comparison	Minimum 4 rats, 8 mice and 2 rabbits for cross-species comparison; 2 dogs for <u>absorption, metabolism, and elimination</u> (AME) = 16	50% (max. savings = 8 if all species included)	<ul style="list-style-type: none"> • Probe AME covers 3 species (rat, mouse, rabbit) • <i>In vivo</i> ADME study also tracks absorption, distribution, time course and elimination of radiotracer • Only metabolism covered <i>in vitro</i> • IVCM has 5 species (pools are n=3 individuals/pool) 	8 (if all species evaluated)

DECISION TREE FOR ANIMAL SAVINGS

Some points to consider when assigning Equivalent Animal Savings...



DECISION TREE FOR ANIMAL SAVINGS DUE TO NAM USE



§ FIRST ? : WHAT IS ENDPOINT(S) OF INTEREST?

§ REGULATORY ACCEPTANCE OF NAM:

§ 2 OUT OF 3 APPROACH FOR SKIN SENSITIZATION

§ SAVINGS = 28 ANIMALS USED IN LLNA

§ INFORMATION SIMILAR TO *IN VIVO* STUDY:

§ ER MODEL + ERTA FOR COMPOUNDS WITH LIMITED METABOLISM (= UTEROTROPIC)

DECISION TREE FOR ANIMAL SAVINGS DUE TO NAM USE

§ DOES THE NAM PARTIALLY FULFILL INFORMATION FROM THE ANIMAL-BASED STUDY?

§ CONSERVATIVE ESTIMATE OF ANIMAL SAVINGS

§ EXAMPLE:

§ USING ANDROGEN RECEPTOR *IN SILICO* MODELS AND ANDROGEN RECEPTOR TRANSACTIVATION ASSAY (ARTA) TO DETECT AR AGONISTS AND ANTAGONISTS

§ *IN VIVO* EQUIVALENT = HERSHBERGER ASSAY:

§ AR AGONISTS/ANTAGONISTS

§ 5ALPHA-REDUCTASE INHIBITORS

§ EVALUATES METABOLITES

§ AR NAMS ≠ HERSHBERGER (48 ANIMALS)

§ EQUIVALENCY SET AT 20% = 9.6 ANIMALS

Does NAM provide full information generated by an *in vivo* comparison study?

↓ No

How does NAM data compare to data generated in the comparison *in vivo* study (i.e., how many *in vivo* endpoints assessed?)

How frequently does the bioactivity assessed by the NAM contribute to positive outcomes in the *in vivo* assay?

Is metabolism adequately considered in the bioactivity assessment in the NAM?

With *in vitro* NAMs, are bioactive concentration, exposure, IVIVE and cytotoxicity/cell stress considered?

What is the level of confidence that NAMs adequately evaluate the relevant bioactivity?

“Animal Savings” equivalent to a subset of animals used in the *in vivo* study (generally favor a conservative estimate)

CALCULATING ANIMAL SAVINGS

§ SOME REPORTING OPTIONS:

§ ABSOLUTE NUMBER OF ANIMAL SAVINGS WITH NAMS

§ PERCENT REDUCTION IN ANIMAL USE

§ PERCENT OF TOXICITY DATA FROM NAMS

§ PERCENT REDUCTION IN ANIMAL USE:

Total animal equivalents = No. of animals used in *in vivo* studies + Equivalent animal savings from NAMS

$$\% \text{ Reduction in animal use} = 1 - \left(\frac{\text{Total animal equivalents} - \text{equivalent animal savings from NAM}}{\text{Total animal equivalents}} \right) * 100$$

CONCLUSION

- § THIS IS DOW'S APPROACH TO ANIMAL USE TRACKING AND ANIMAL USE SAVINGS BASED ON NAMS
 - § NAM INFORMATION HAS VALUE
 - § VALUE DEPENDS ON HOW DATA ARE USED
 - § LEVEL OF CERTAINTY
- § STARTING POINT: LIKELY IMPROVEMENTS OR ADAPTATIONS TO THIS APPROACH

Thank You!

QUESTIONS?