Anti-inflammatory options for cattle & swine

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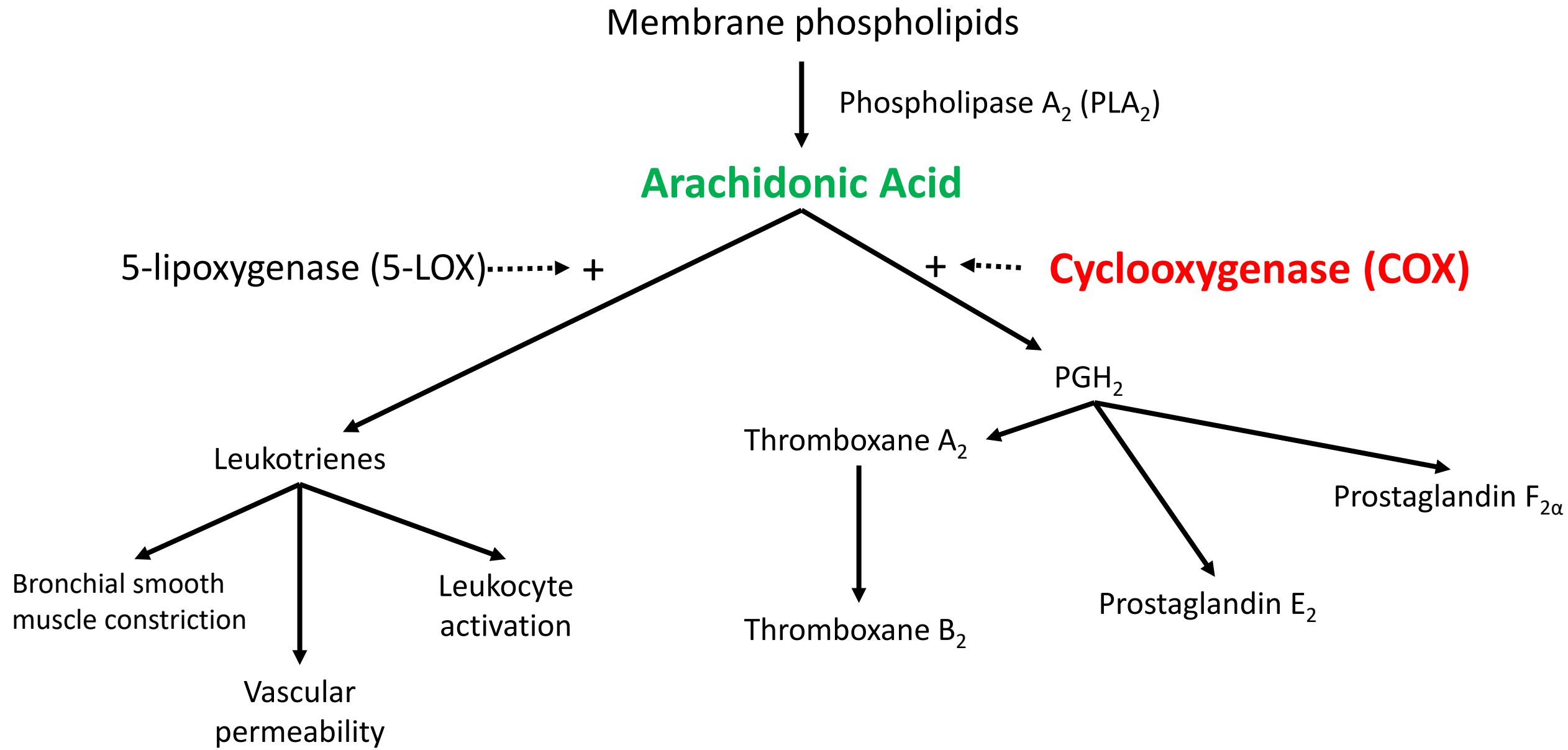
Conflict of Interest

I have received funding from Merck Animal Health

Arachidonic acid pathway



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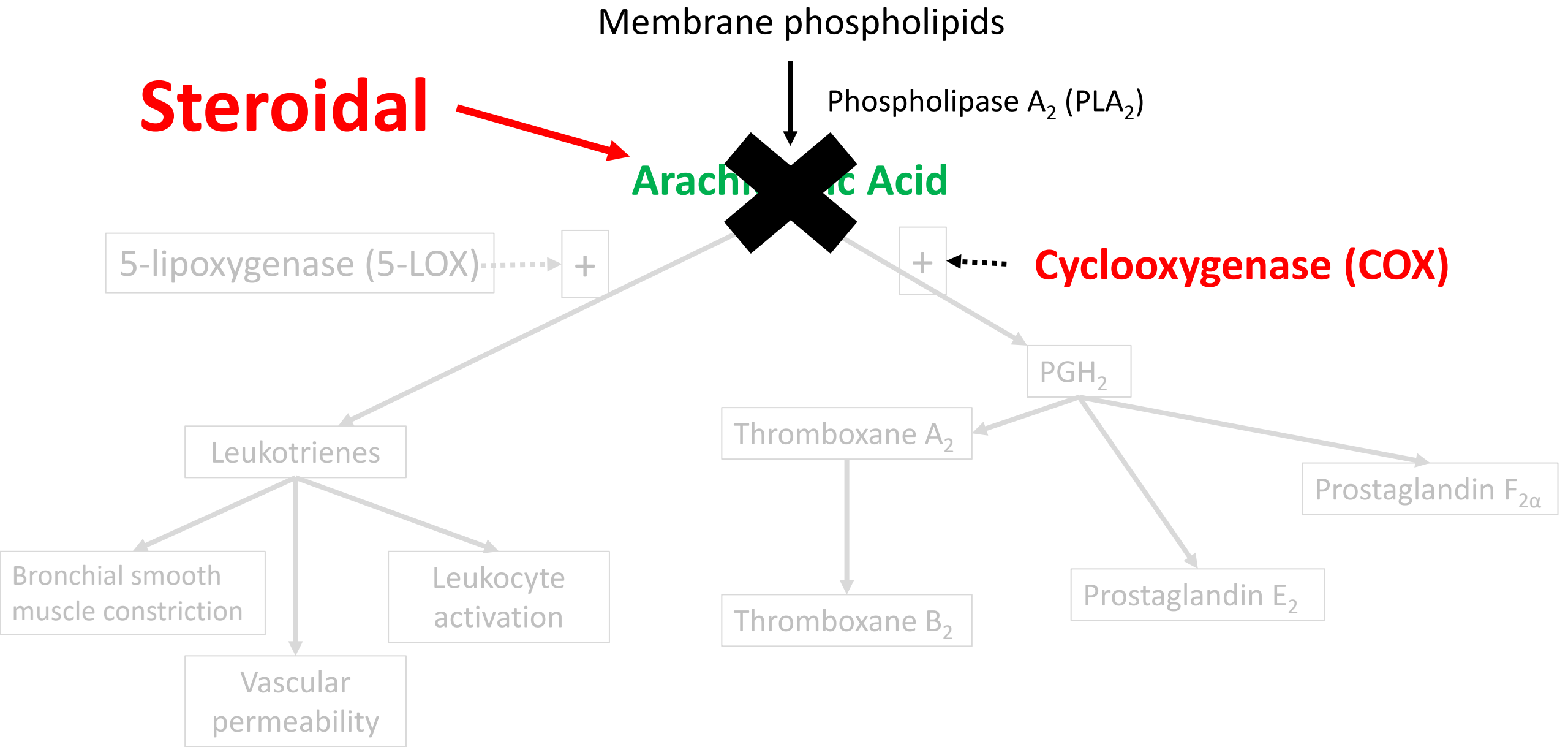

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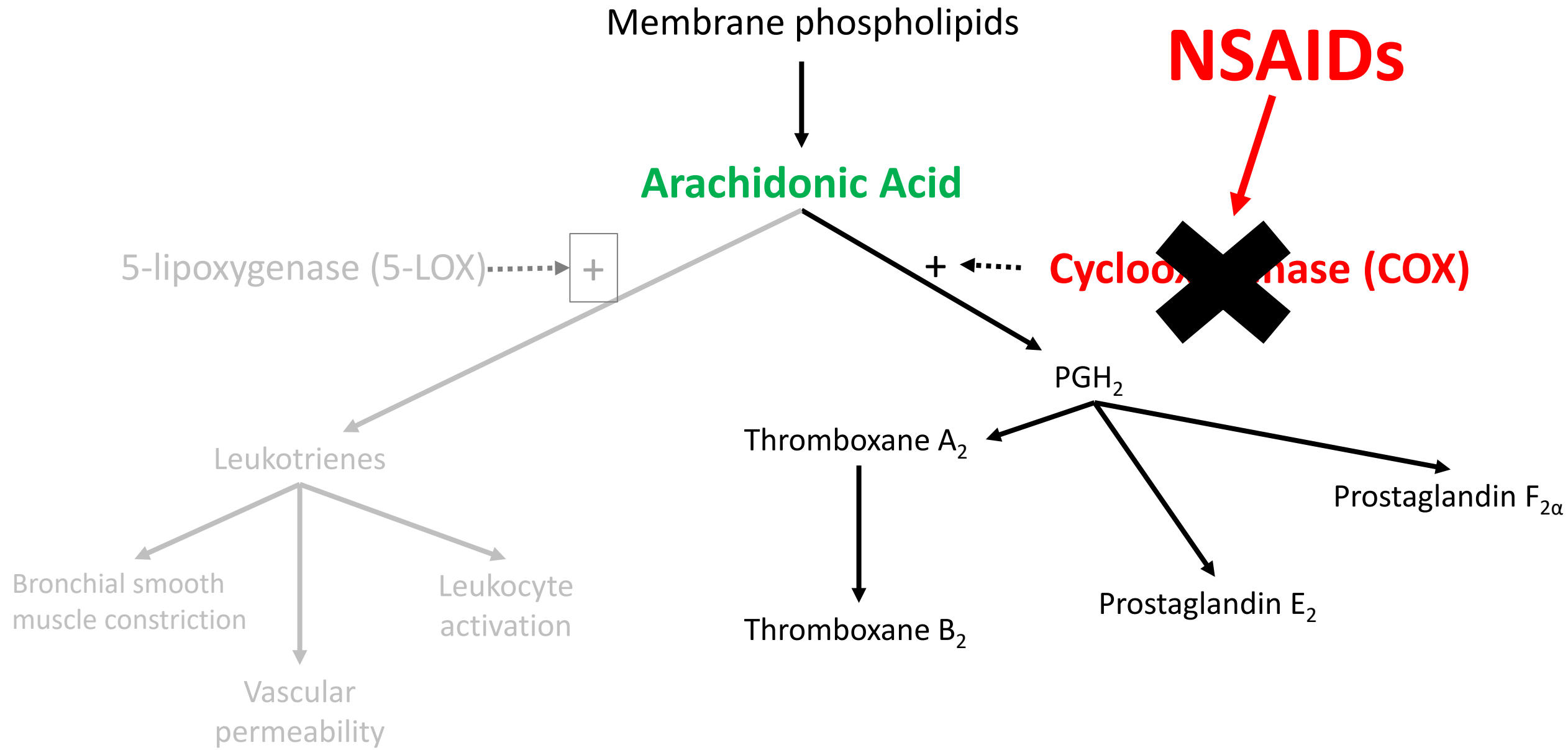


Cyclooxygenase (COX)

COX-1

- Constitutive in tissues
- “housekeeping’ functions
- Gastroprotection, renal blood flow, and hemostasis
- Nonselective NSAID inhibition
  - Aspirin

COX-2

- Constitutive in select tissues
- Induced expression
  - Proinflammatory prostaglandins
- COXIB’s are selective inhibitors

Anti-inflammatory drugs approved for group medication in the US

Dear Veterinarian Letter regarding use of aspirin products in lactating dairy cattle

Dear Veterinarian:

The U.S. Food and Drug Administration understands that veterinarians and dairy farmers may be treating lactating dairy cattle for pyrexia and pain with aspirin and wants to clarify that there are no FDA-approved aspirin products for use in cattle. The extralabel use of unapproved drugs in food-producing species is prohibited.

There are FDA-approved products for controlling pyrexia and pain in lactating dairy cattle that are safe, effective, and have established milk and meat withdrawal periods. All FDA-approved animal products are required to carry one of the following statements on the label:

"Approved by FDA under NADA # XXX-XXX" (for brand name animal drugs), or

"Approved by FDA under ANADA # XXX-XXX" (for generic animal drugs).

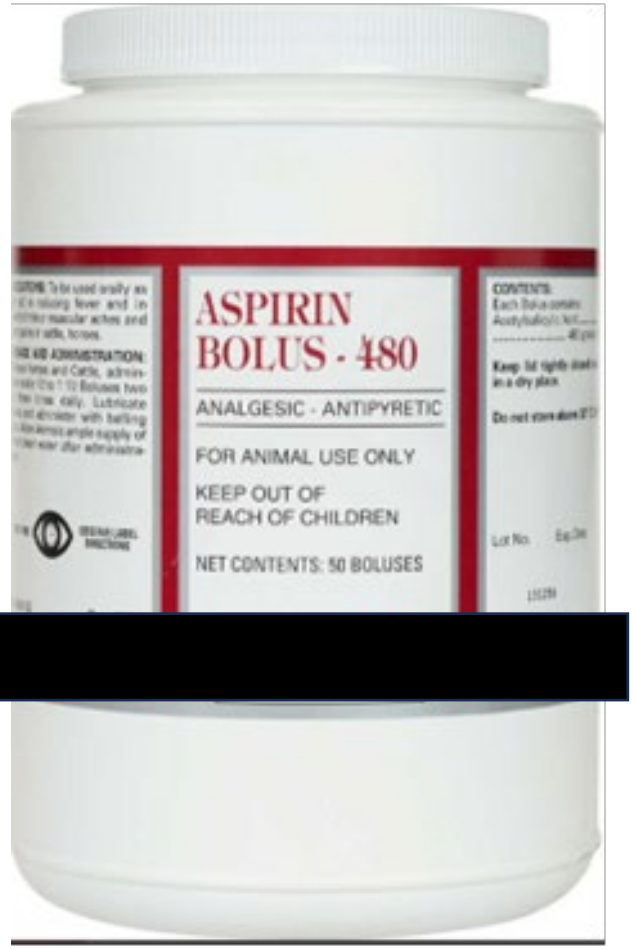
Under the Animal Medicinal Drug Use Clarification Act (also known as AMDUCA), veterinarians may use an FDA-approved human or animal drug in food-producing species under specific conditions. There is one FDA-approved human aspirin product (Vazalore) that is currently marketed. Although other human aspirin products are marketed under an over-the-counter monograph, that monograph is not an approval and, therefore, these products cannot be used in an extralabel manner. Given the impracticality of dosing cattle with a sufficient amount of the approved human product, the FDA understands that veterinarians and dairy farmers may instead be using unapproved aspirin products that are not legally marketed. The extralabel use of unapproved drug products in food-producing species is prohibited.

Veterinarians and dairy farmers should stop use of unapproved aspirin in lactating dairy cattle and use FDA-approved products to control pyrexia and pain. In the event that animals have already been treated with aspirin, veterinarians should use their scientific expertise and available resources to set protective and extended milk and meat withdrawal periods for treated animals.

11 Oct 2024

What does this mean??

- There is **NO** legal pathway to use acetylsalicylic acid or sodium salicylate in cattle or swine (or really any food animal) using product marketed for those species.
- Does NOT matter if manufactured under “GMP standards” or in a “FDA Inspected” facility.
- Listing on the USDA National List of Allowed and Prohibited Substances does **NOT** mean it is legal either!
- No group option for anti-inflammatory medication
  - Available? Yes
  - Legal? No practically/there better options


ASPIRIN
BOLUS - 480
ANALGESIC - ANTIPYRETIC
FOR ANIMAL USE ONLY
KEEP OUT OF
REACH OF CHILDREN
NET CONTENTS: 50 BOLUSES

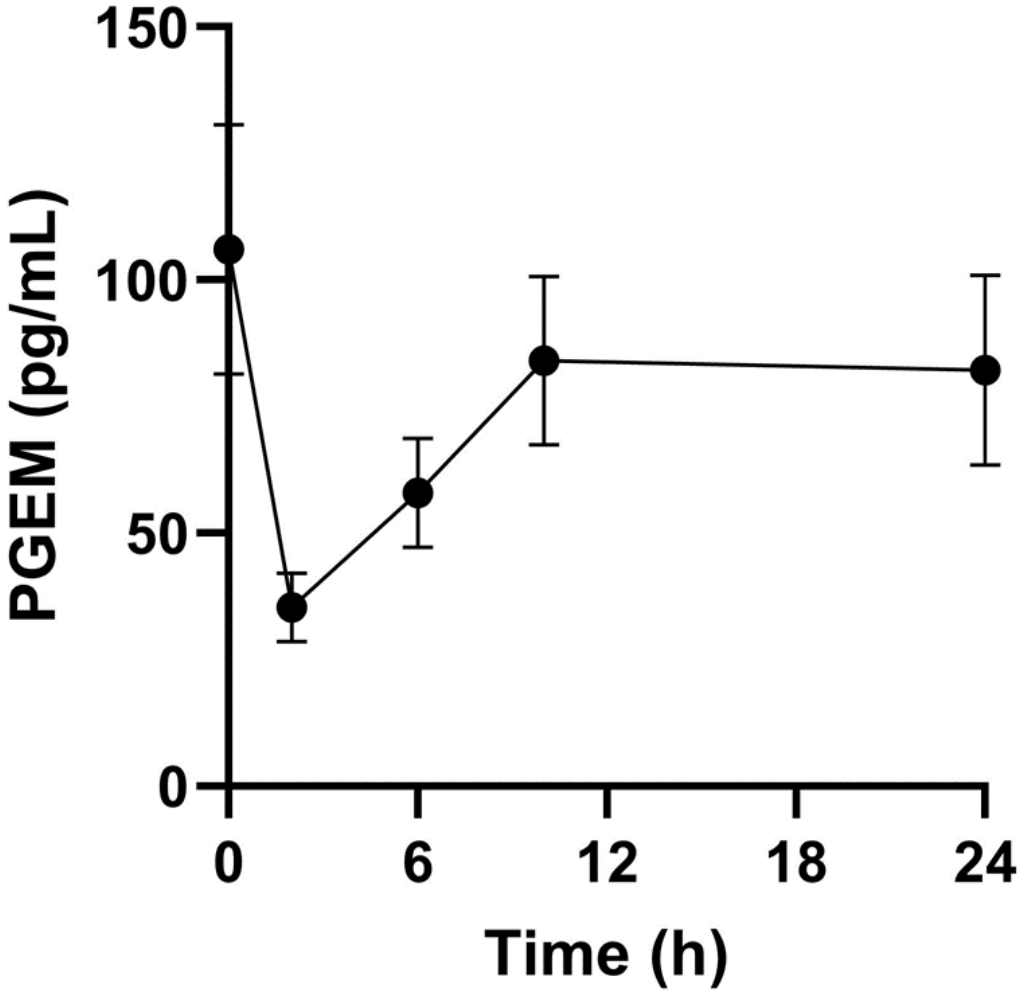

Sodium Salicylate
Concentrate 48.6% w/v
For Use in Livestock Only
Keep Out of Reach of Children
1 Gallon (3.79 Liters)

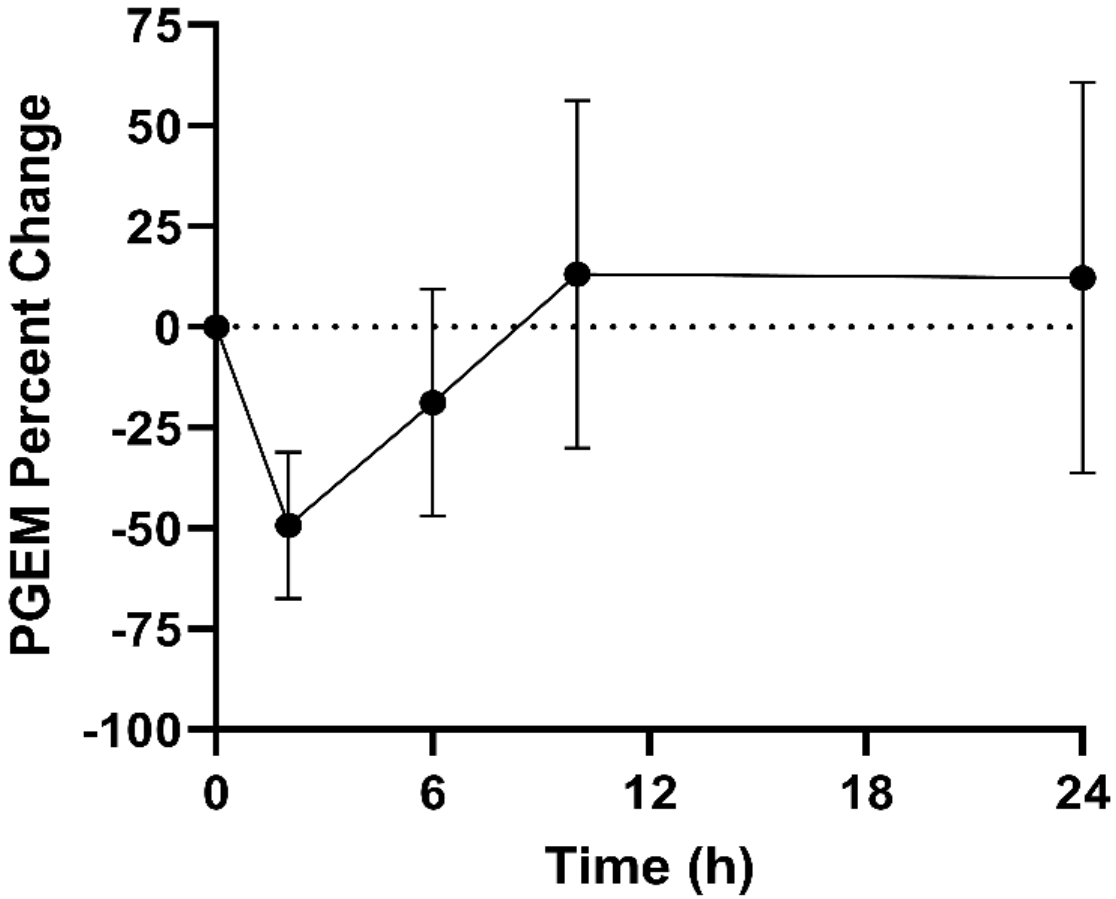

IRIN
S - 480
TIPYRETIC
KEEP O
REACH OF
NET CONTENTS:


Sodium Sa
Concentrate 48.

Results – Plasma PGEM

Two treatments at
200 mg/kg PO q24hr





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Error bars represent standard deviation

Fritz et al. JDS

In theory….it's not a hard no…

- Vazalore (81 mg) is FDA approved
  - Well known retail outlet has it for $14.97/30 capsules
- 100 lb dairy calf at 200mg/kg q 6 h
  - 9090 mg per dose or 112 capsules
  - 448 capsules or 15 bottles for 24 hours
  - $225 for aspirin therapy
- A mature dairy cow would need 21 bottles!!!
  - And have a 108-h milk withhold!

Implications of ELDU in food animals

- ELDU is permitted only by or under the **supervision of a veterinarian** with a valid **Veterinarian/Client/Patient Relationship**
- ELDU is allowed only for **FDA approved animal and human drugs.**
- ELDU for **therapeutic purposes** only (animal's health is suffering or threatened).
  - Not for production use (increased milk production).
- ELDU is not permitted if it results in a **violative food residue**, or any residue which may present a risk to public health.

Can I do some good?

Can I do some harm?

Can I get it in the animal?

What are the costs?

Mike Apley

Anti-inflammatory Drugs - Cattle

Drug	FDA Approved formulations	Therapeutic data	Withdrawal data?
Aspirin	No	No	No
Phenylbutazone	Yes	No	No
Carprofen	Yes	Limited	No
Firocoxib	Yes	Limited	No
Ketoprofen	Yes	Yes	Yes
Flunixin	Yes	Yes	Yes
Meloxicam	Yes	Yes	Yes
Dexamethasone	Yes	Yes	Yes

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Ketoprofen	Yes	Yes	Yes
Flunixin-S	Yes	Yes	Yes
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Dexamethasone	Yes	Yes	Yes

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Flunixin formulations

Flunixin meglumine

- FDA approved formulations for cattle and swine
  - Injectable: cattle and swine
  - Transdermal: cattle only
- Combinations with oxytetracycline or florfenicol are approved for cattle.

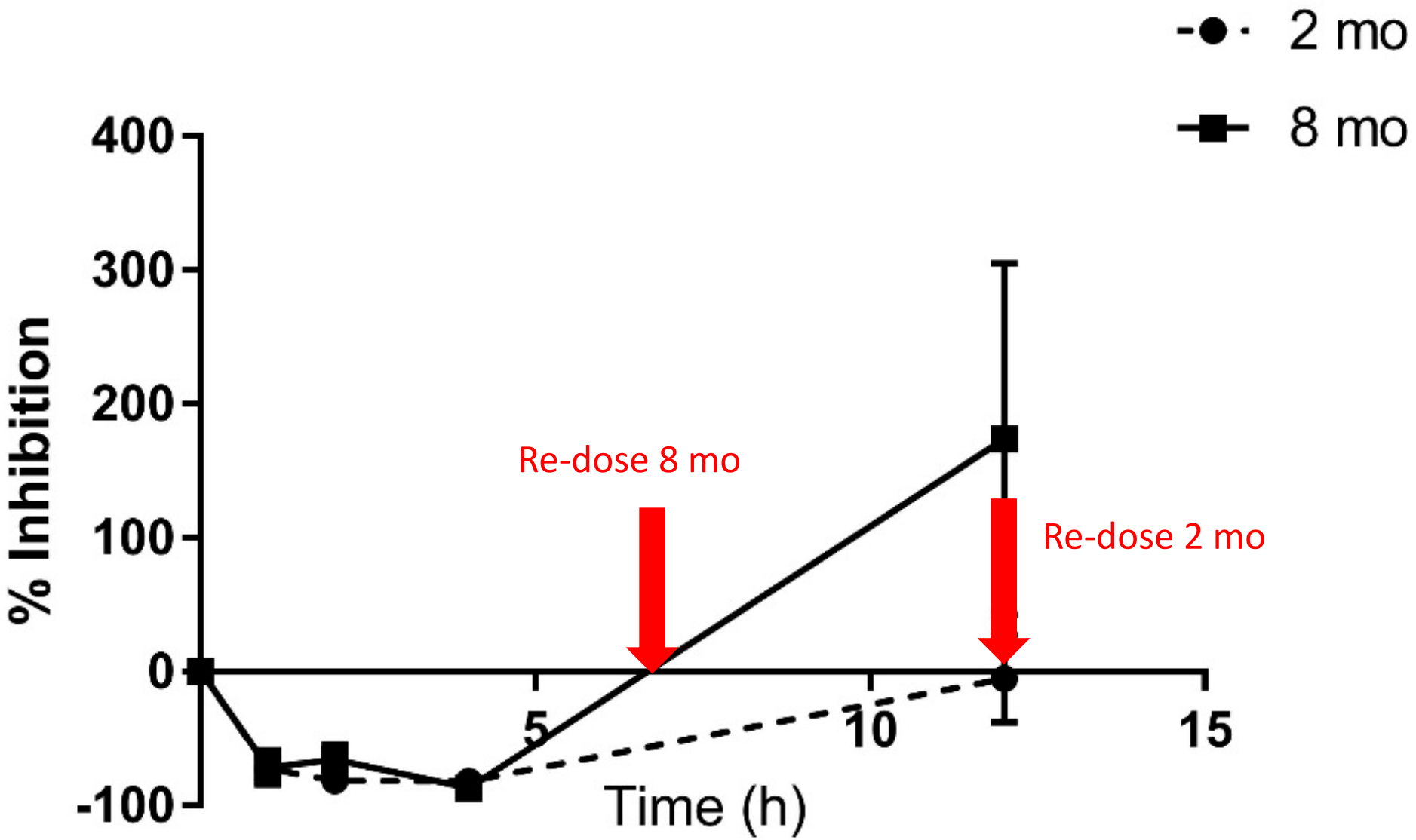
Flunixin meglumine – Injectable

- FDA approved formulations for cattle (including dairy cattle) and swine
  - Cattle: Banamine® and many generics
  - Swine: Banamine-S ® and generics (also with a “-S”)
- Indications:
  - Cattle: control of pyrexia associated with bovine respiratory disease, acute bovine mastitis, and endotoxemia. Control of inflammation associated with endotoxemia.
  - Swine: control of pyrexia associated with swine respiratory disease

Flunixin meglumine – Injectable

- Injectable
  - Cattle: IV only (other routes cause muscle damage)
  - Swine: IM in the neck following PQA
- Injectable formulation has 4-12 hours of efficacy
  - Give 2-3 times per day for full effect
  - Depends on the age of the animal
- Withholds:
  - Meat: 4 days in cattle and 12 days in swine
  - Milk: 36 hours for bovine milk

PGE_2



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May 2018

Banamine® Transdermal

- Indications: Control of pyrexia associated with BRD and acute mastitis and control of **pain** **associated with foot rot**

8 day meat hold

48 h milk hold

Banamine® Transdermal

- EASY to administer!!!
  - Pour along calf's back
- Do NOT use on wet hide and protect from rain for 6 hours after dosing
- Wear gloves when administering

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Meloxicam

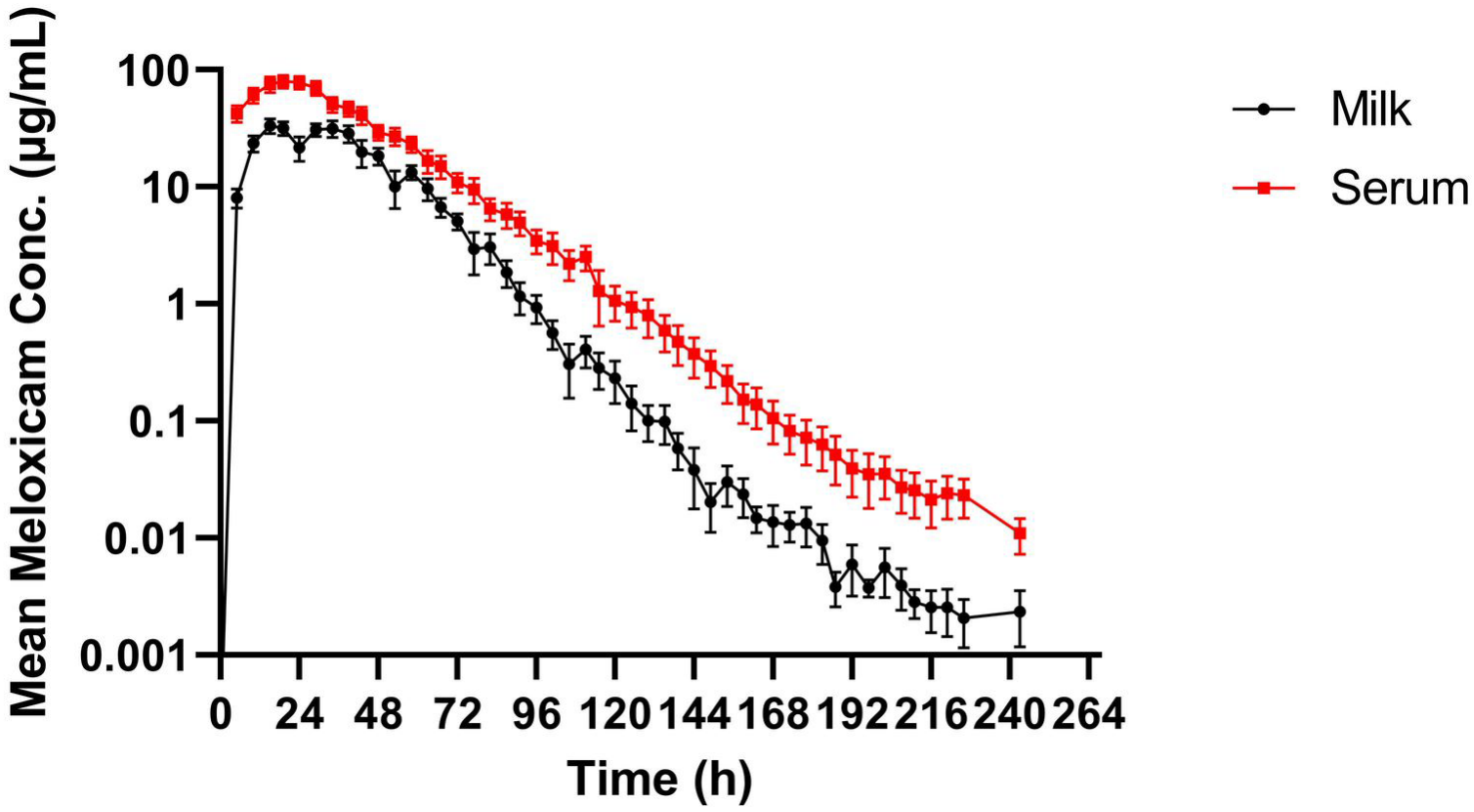
- NO label approvals in the US
- Allowed as ELDU with VCPR
- All uses are ELDU
  - ZERO residue tolerance
  - FSIS method @ 10 ng/g

Meloxicam

- Dose: 1 mg/kg or 3 - 15 mg tabs per 100 pounds
- Administer orally
  - Gelatin capsules.
  - Dissolve in water and administer
  - *<u>Individual</u>* feed pan

Meloxicam Safety - Fritz et al. 2023

- Single dose at **30 mg/kg** to 5 cows
- No adverse effects observed in 4 cows



Ketoprofen

Approved April 2021 by Zoetis

Indications: control of pyrexia associated with BRD

Dose: 3 mg/kg (1 mL/74 lb) SubQ

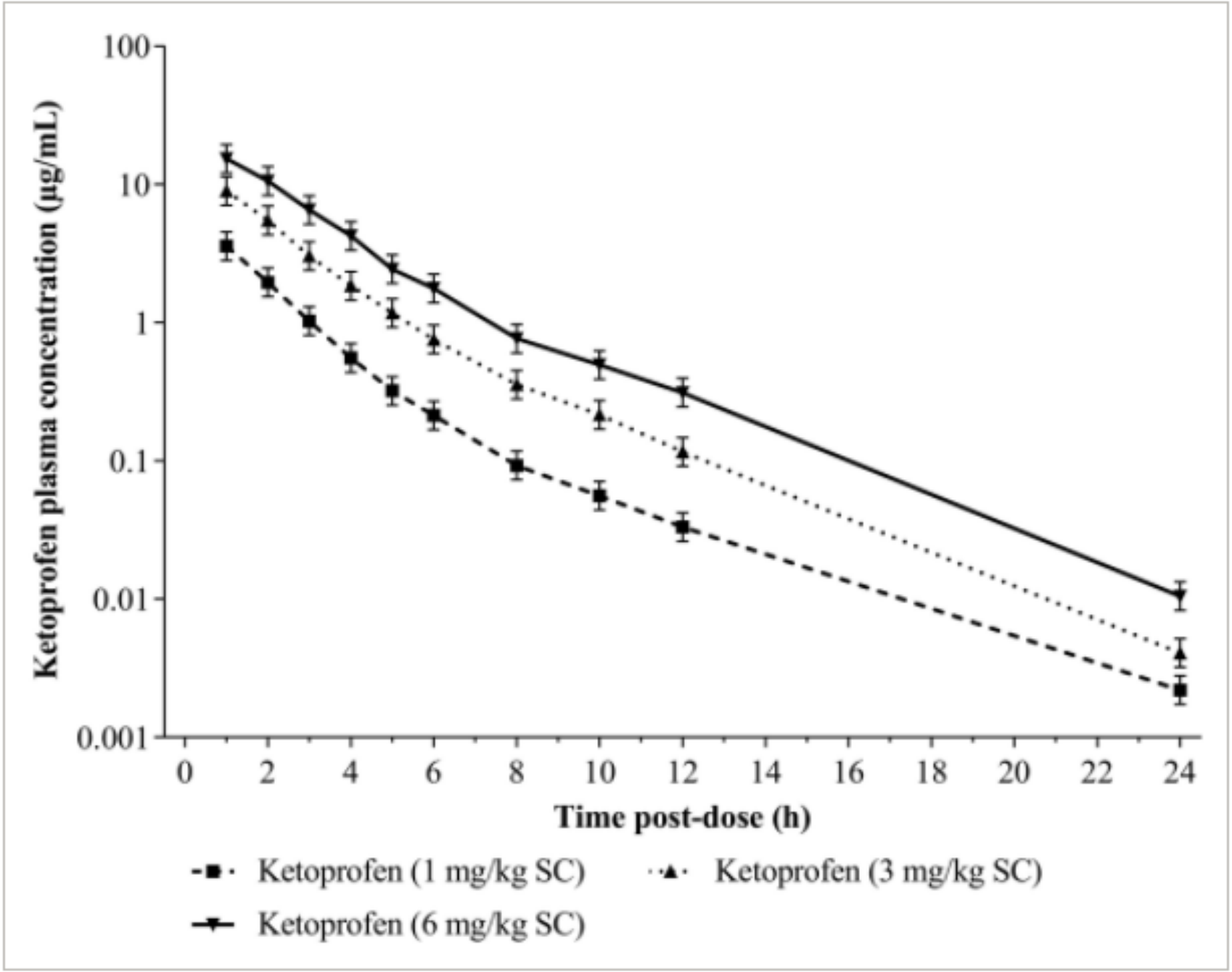
Can be administered q24 h for 3 days

Meat hold: 48 hours

Ketoprofen

3 mg/kg SQ

Cmax 8.97 µg/mL
Half-life 2.5 h



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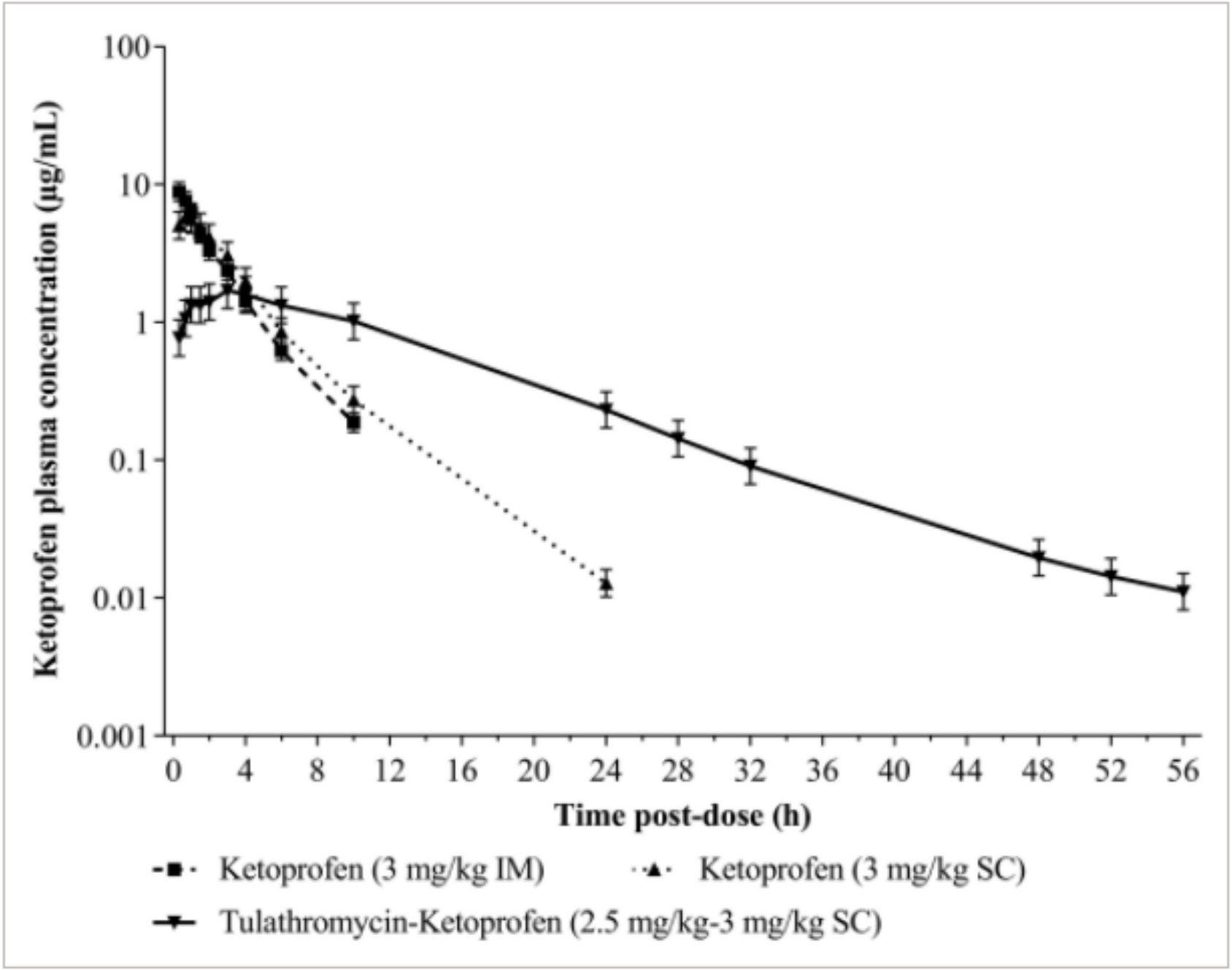
Ketoprofen



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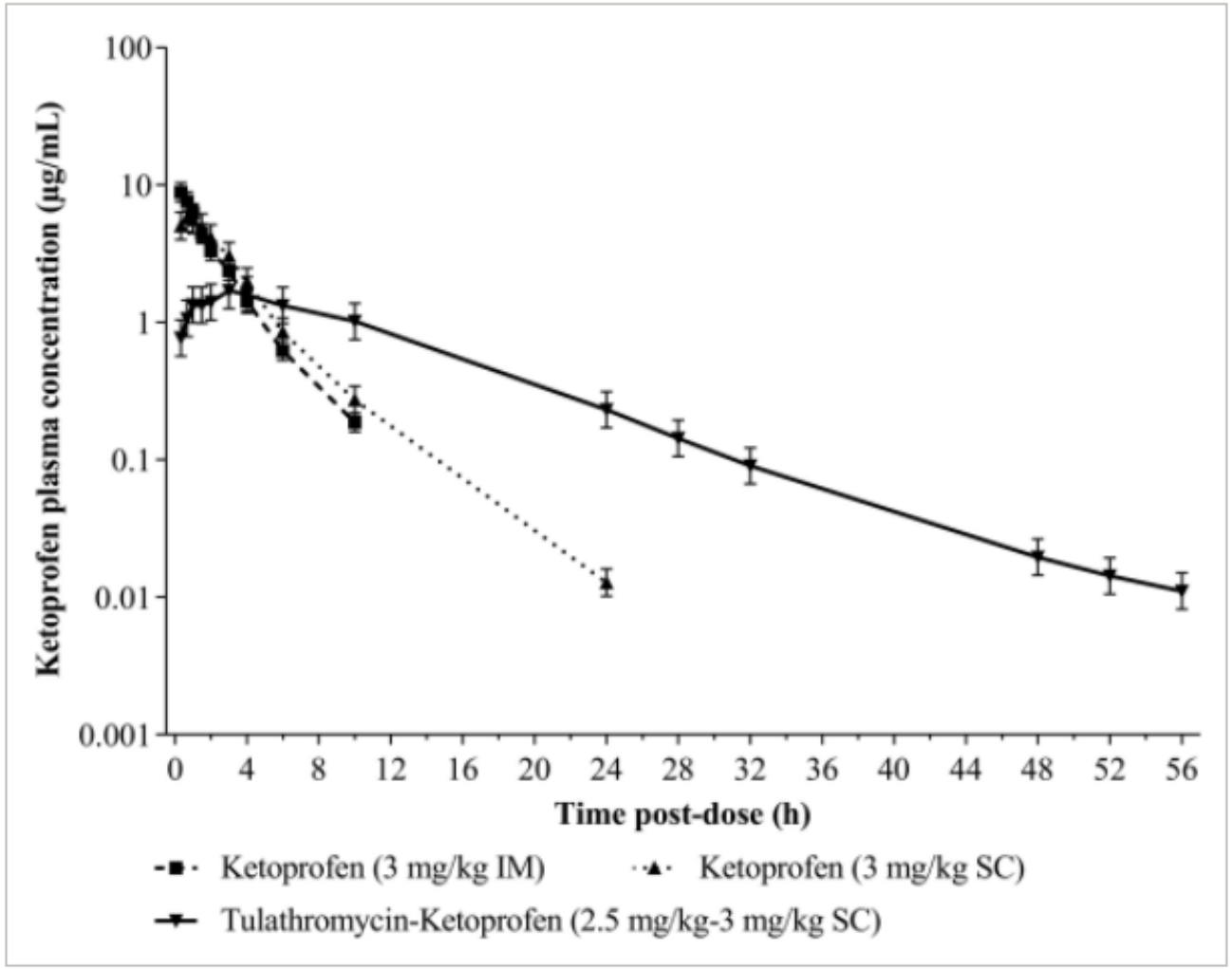
Ketoprofen

3 mg/kg SQ

	Keto	Keto+abx
Cmax (µg/mL)	6.3	2.1
Half-life (h)	2.5	6.8
Tmax (h)	0.8	4



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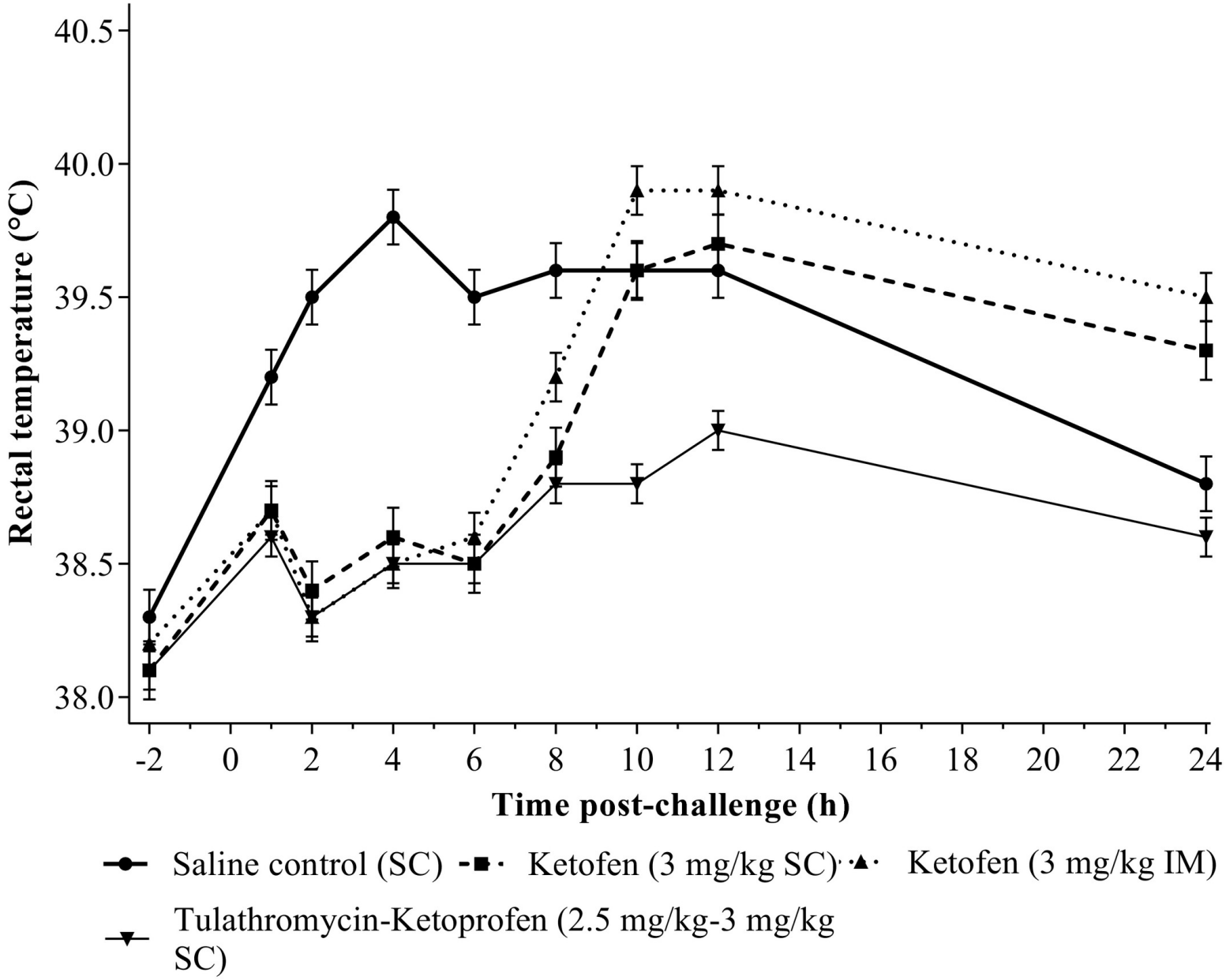
Ketoprofen

LPS Challenge

<12 h of pyrexia control with monotherapy



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Firocoxib

- COX-2 selective NSAID
- Oral veterinary formulations
  - Generic approved March 2022
- For cattle dehorning: as effective as meloxicam at 2 mg/kg (Stock et al., 2021)
- For swine: transmammary delivery to nursing piglets resulted in reduced stress and increased ADG at 2 mg/kg IM (Coetzee et al., 2019)

Dexamethasone

- Antipyretic
- Anti-inflammatory
- Protein catabolism
- Transient hyperglycemia from gluconeogenesis
  - Useful in dairy cattle with ketosis?
  - Maybe the transient decrease in milk production??
- Label dose of 5-20 mg in cattle given IM or IV
- No withdrawal time on label

Dexamethasone

- Immunosuppression in cattle
  - 0.04 mg/kg IM for 3 days leads to neutrophil inhibition
  - Single doses may have this effect
- Immunosuppression in swine
  - Higher dose required – 2 mg/kg
- Interference with Interferon-gamma and interleukin-2 production from T-cells.
- Reactivates latent Bovine Herpesvirus-1 (IBR)

Dexamethasone – Adverse Effects

- Bull sterility due to semen defects
- Immunosuppression
- Abortion in cows
  - When would we want to take advantage of this?

Questions??

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