SAVING ASIA'S VULTURES
FROM EXTINCTION

SAVE

NSAID Alert! Symposium

2016

Welcome

Dr. Homi Khusrokhan

President, BNHS

(Bombay Natural History Society)

Welcome

Prof. David Houston

Chairman, SAVE

(Saving Asia Vultures from Extinction)

Welcome

Mr. C. Arunachalam

Deputy Drug Controller,

Drug Controller Generals Office,

India

Release ceremony

Aceclofenac: a vulture-toxic drug

- Mr. C. Arunachalam, Drug Controller General Office, India

Ketoprofen: a vulture-toxic drug

- Mrs. N. Sultana, Directorate General of Drug Administration, Bangladesh

Nimesulide: a vulture-toxic drug

- Mr. K. C. Santosh, Department of Drug Administration, Nepal

Flunixin: a vulture-toxic drug

- Dr. M. Aslam, Drug Regulatory Authority, Pakistan

SAVING ASIA'S VULTURES
FROM EXTINCTION

SAVE Partners

BCN

ICBP

NTNC

Pakistan

Key Supporting Agencies

Ministry of Environment, Forest and Climate Change (India)
Pakistan Forest Department
Forest Department, People's Republic of Bangladesh
Ministry of Forest and Soil Conservation, Nepal
Ministry of Agriculture Forestry & Fisheries (Cambodia)
Haryana State Forest Department
West Bengal Forest Department
Assam Forest Department
Madhya Pradesh Forest Department
Central Zoo Authority (India)
Nepal Department of National Parks & Wildlife Conservation
Forestry, Wildlife & Fisheries department, Punjab Province
IUCN Bangladesh Country Office

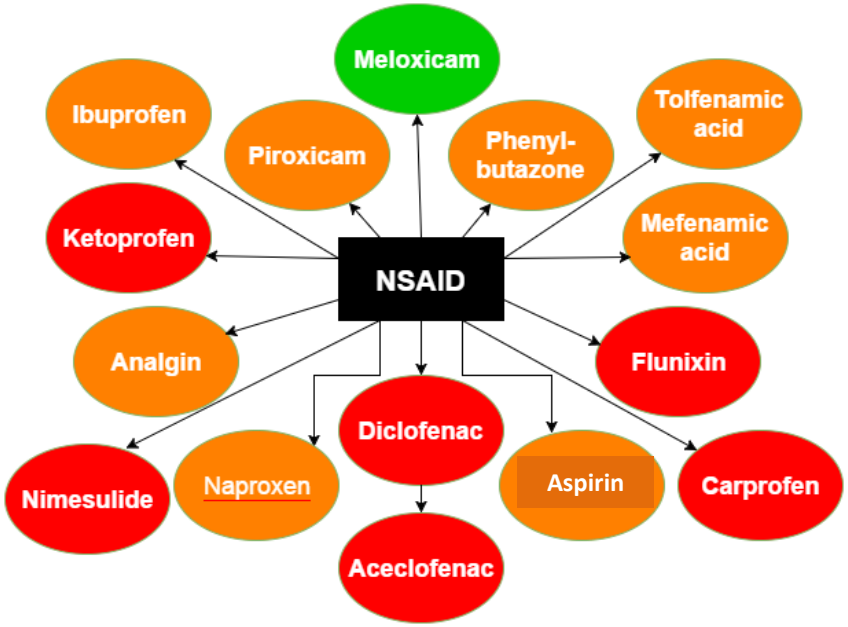
NSAID Alert!

Evidence that NSAIDs, other than diclofenac, are toxic or probably toxic to *Gyps* vultures

Presented by
Dr. Toby Galligan,
Senior Conservation Scientist,
RSPB Centre for Conservation Science, UK

The bigger problem

- Diclofenac is not the only veterinary NSAID available in South Asia



- Only one, meloxicam, has been shown to be not toxic to *Gyps* vultures
- Eight are of an unknown toxicity to *Gyps* vultures
- Five are toxic or probably toxic to *Gyps* vultures
- Evidence for these toxic and probably toxic NSAIDs is what we present in this symposium

The bigger problem

- We need bans on all NSAIDs that are toxic to *Gyps* vultures
- Without bans
  - We are releasing captive-bred *Gyps* vultures into hazardous environments
  - All *Gyps* vultures that we release may die prematurely
  - South Asia's three critically endangered *Gyps* vultures may become extinct in the wild

- How we can bring about such bans throughout South Asia is what we would like to discuss later today

Types of evidence

- Clinical evidence
  - Cases of therapeutic use of NSAIDs
    - *Gyps* vultures
    - Non-*Gyps* vultures
    - Carnivorous birds
- Field evidence
  - Post mortem examinations of dead *Gyps* vultures
- Experimental evidence
  - Pharmacokinetics studies (absorption, elimination and metabolism)
    - domesticated ungulates
    - *Gyps* vultures
  - Safety tests: next slide

Safety testing (experimental evidence)

- Exposing a *Gyps* vultures to a NSAID
  - oral dose
  - tissue feed from a treated animal (cattle, buffalo)

- Maximum level of exposure (MLE) used
  - The largest dose likely to be encountered (i.e., worst case scenario)
  - Calculated assuming that cattle in India are typically dosed twice the recommended amount (apparent in surveys of cattle carcasses)

- MLE = the highest tissue-specific residue concentration of the NSAID in cattle x the weight of a large meal for a given vulture species ÷ the body weight of that same vulture species

Safety testing (experimental evidence)

- Examine
  - Observable symptoms
  - Concentrations of biochemicals in blood
  - Death
  - Necropsy and pathology
  - NSAID concentrations in tissues

- Compare the above effects with those of *Gyps* vultures not exposed to the NSAID (controls)

Diclofenac

Vulture-toxic drug #1

Presented by
Dr. Vibhu Prakash,
Deputy Director & Principal Scientist,
BNHS, India

Diclofenac
Experimental evidence

- Diclofenac safety test in *Gyps* vultures in Pakistan and South Africa
  - Oaks et al. (2004), Swan et al. (2006a)

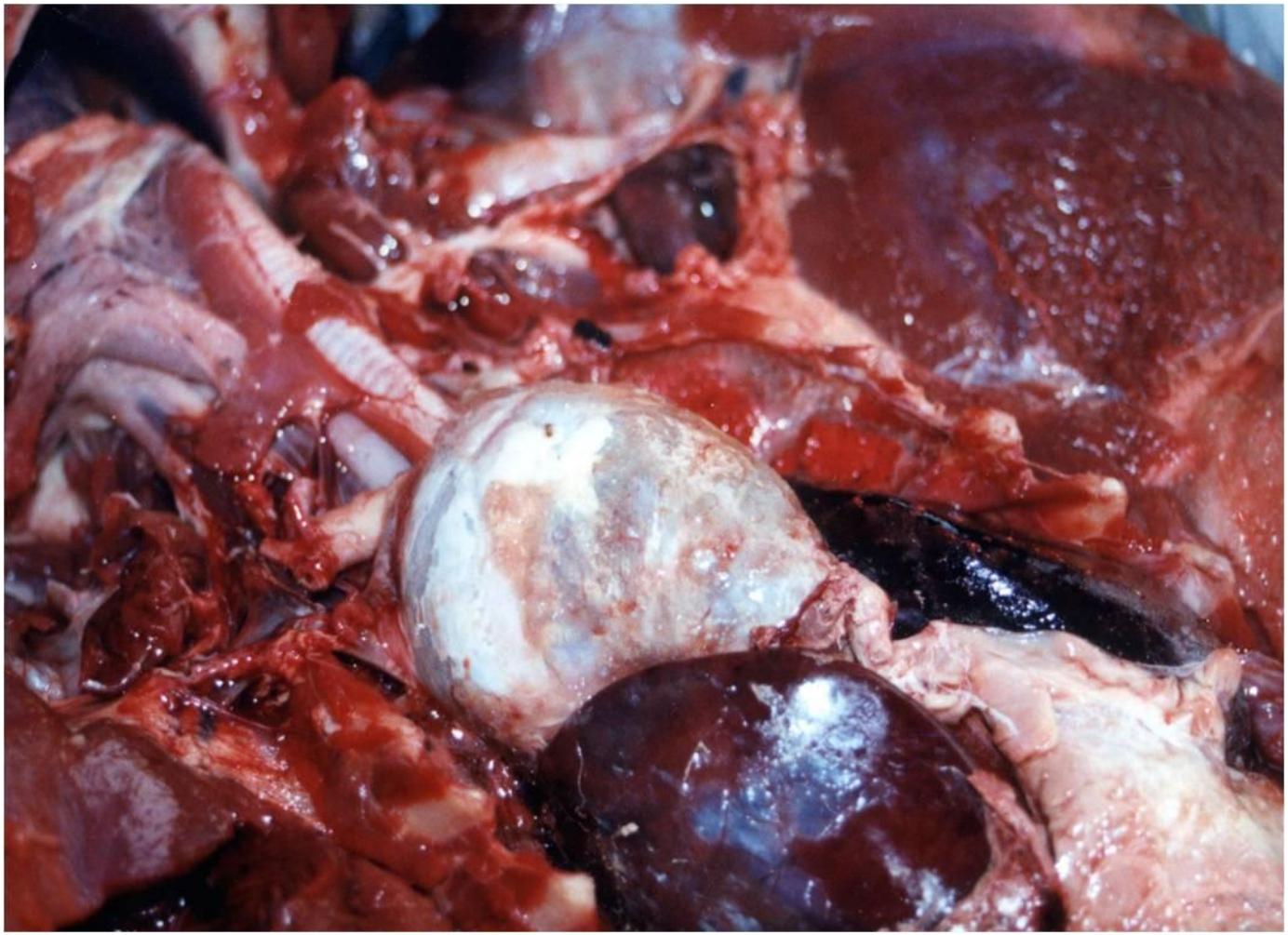
- Asian white-backed vulture *Gyps bengalensis,* African white-backed vulture *Gyps africanus* and Eurasian griffon vulture *Gyps fulvus* used
- The maximum level of exposure (MLE) to diclofenac for an Asian white-backed vulture is 1.22 mg/kg body weight (bw)

- Doses below the MLE (0.8-1.0 mg/kg bw) killed 15 out of 15 vultures
- Doses further below the MLE (0.1-0.6 mg/kg) killed 2 out of 4 vultures
- Doses far below the MLE (<0.01-0.03 mg/kg) killed 1 out of 6 vultures

Diclofenac
Experimental evidence

- All vultures that died showed
  - Greatly elevated uric acid concentration in plasma before death
  - kidney damage and visceral gout (clinical signs of renal failure in birds) at post mortem
- All three species were affected similarly

- *Diclofenac is toxic to* Gyps *vultures at a dose below the MLE*



Diclofenac
Field evidence

- Survey of dead wild *Gyps* vultures in India, Nepal & Pakistan 2000-2004
  - Oaks et al. 2004, Shultz et al. 2006
  - 259 wild *Gyps* vultures found dead
  - 237 (83%) vultures had visceral gout

- Tissue analysis for diclofenac in 56 of these vultures
  - 39 out of 39 vultures (100%) that tested positive for diclofenac had visceral gout
  - 17 out of 17 vultures (100%) that tested negative for diclofenac did not have visceral gout

- *Diclofenac is causing renal failure and death in* Gyps *vultures in the wild*

Diclofenac
Summary of evidence

- Safety testing has shown diclofenac at doses below the MLE causes visceral gout and death in *Gyps* vultures

- Post mortem examination of wild *Gyps* vultures found dead in the field have shown diclofenac residues in association with visceral gout

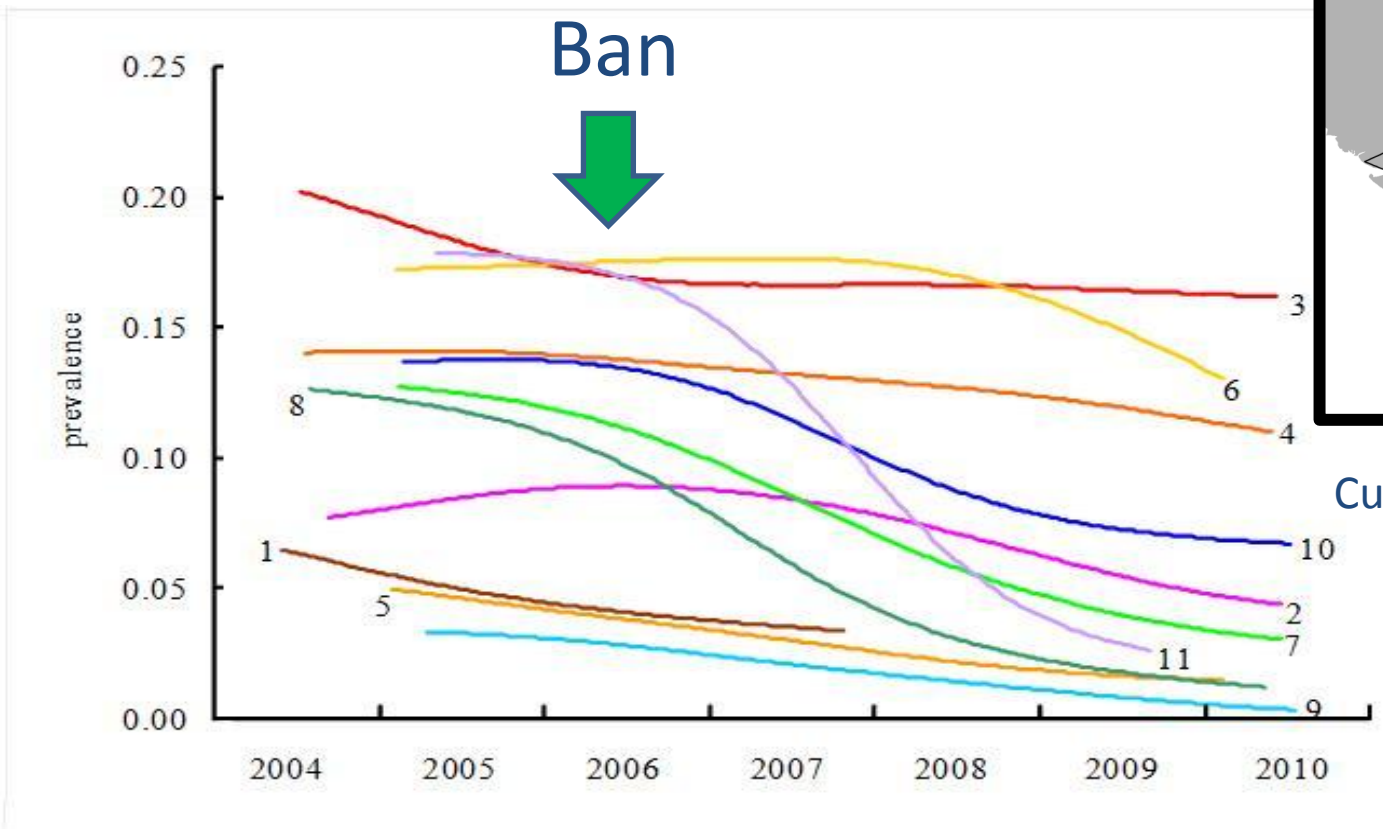
- Therefore, wild *Gyps* vultures are exposed to lethal concentrations of diclofenac in domesticated ungulate carcasses where this drug is used for veterinary purposes in South Asia

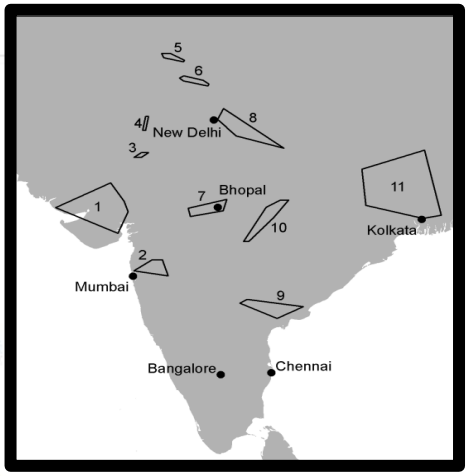
Bans on diclofenac

- Based on this evidence
  - In 2006, licences to manufacture veterinary diclofenac withdrawn in India, Nepal and Pakistan
  - In 2010, licence to manufacture veterinary diclofenac withdrawn in Bangladesh
  - In 2015, licence to manufacture veterinary diclofenac withdrawn in Iran

  - In 2015, manufacture of human diclofenac restricted to single-dose vials in India

Effect of ban: cattle carcasses

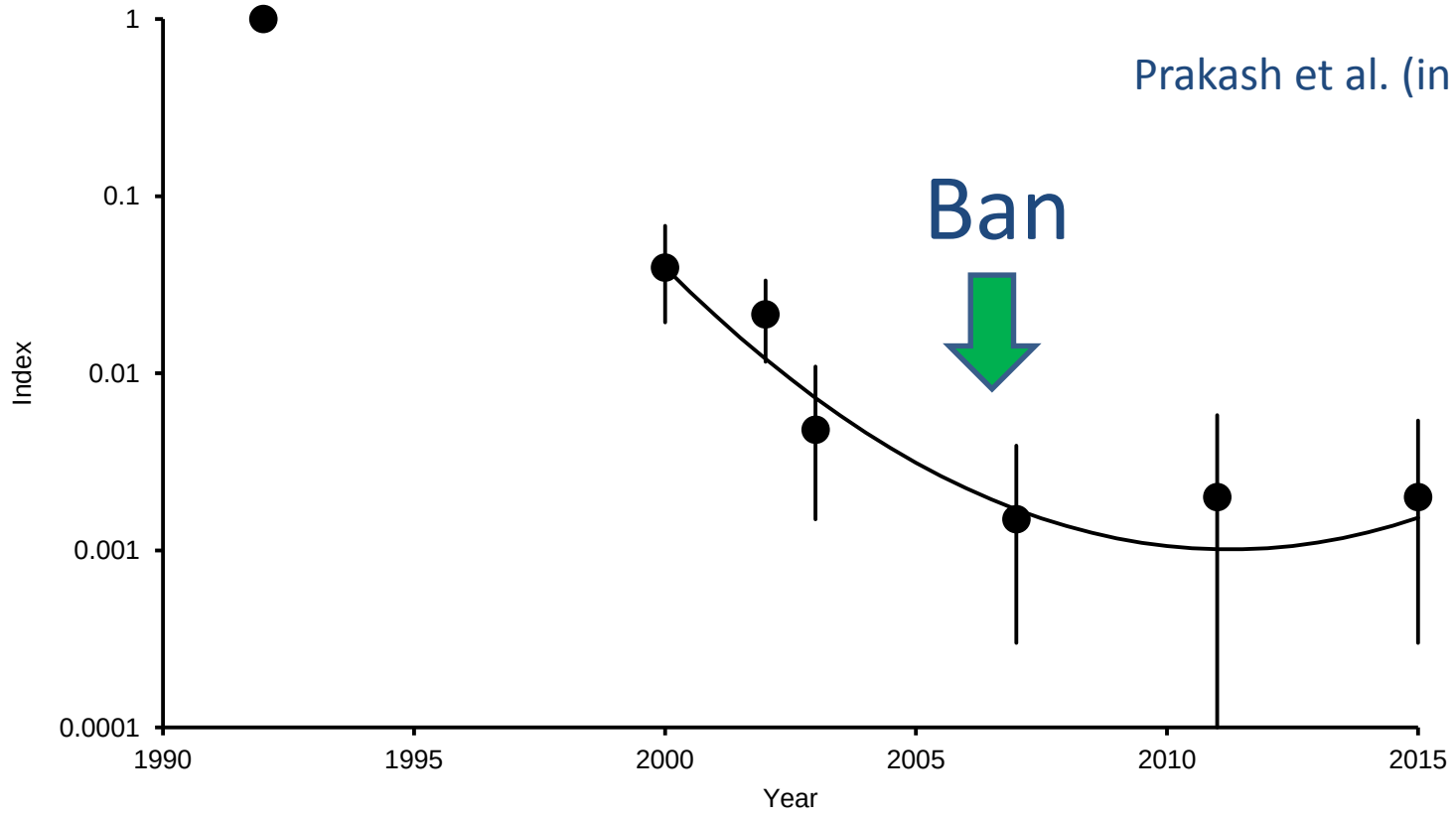




Cuthbert et al. (2014)

- Repeated surveys of cattle carcasses in carcass dumps in India
- Proportion of carcasses with diclofenac residue declined after the ban in 11 out of 11 regions surveyed
- However, the extent of decline varied among the 11 regions

Effect of ban: vulture populations



- Population trend of Asian white-backed vulture *G. bengalensis* in India
- 99.9% decline between 1992 and 2007 (before ban)
- Rate of decline has slowed after the ban in 2006
- Similar trends seen in other countries and other *Gyps* species

Diclofenac ban
Summary

- Based experimental and field evidence, veterinary diclofenac was banned in five countries with *Gyps* vultures

- In India, the ban has reduced the
  - Proportion of cattle carcasses with diclofenac residue
  - Proportion of dead *Gyps* vultures with diclofenac residue
  - Rate of population decline in *Gyps* vultures

- Similar responses in Nepal and Pakistan

Diclofenac ban
Summary

- But,
  - Vultures are still being found dead
  - Vulture declines may be continuing (estimates imprecise)
  - Vulture populations are small
    - 5,700 *G. bengalensis*
    - 11,500 *G. indicus*
    - 1,400 *G. tenuirostris*

    (Prakash et al. in review)

Meloxicam

Vulture-safe drug

Presented by

Dr. Devendra Swarup,

Formerly Director, ICAR-CRIG &

Head, Med. Div. ICAR-IVRI, India

Meloxicam
Clinical evidence

- Questionnaire on NSAID use and outcome in birds at zoos and wildlife centres worldwide
  - Cuthbert et al. 2007

- Meloxicam caused no mortality in 39 out of 39 cases involving *Gyps* vultures (6 species)
- Meloxicam caused no mortality in 700 out of 700 cases involving other vultures, raptors and scavenging birds (54 species)

- *Meloxicam at therapeutic doses is not toxic to* Gyps *vultures*

Meloxicam
Experimental evidence

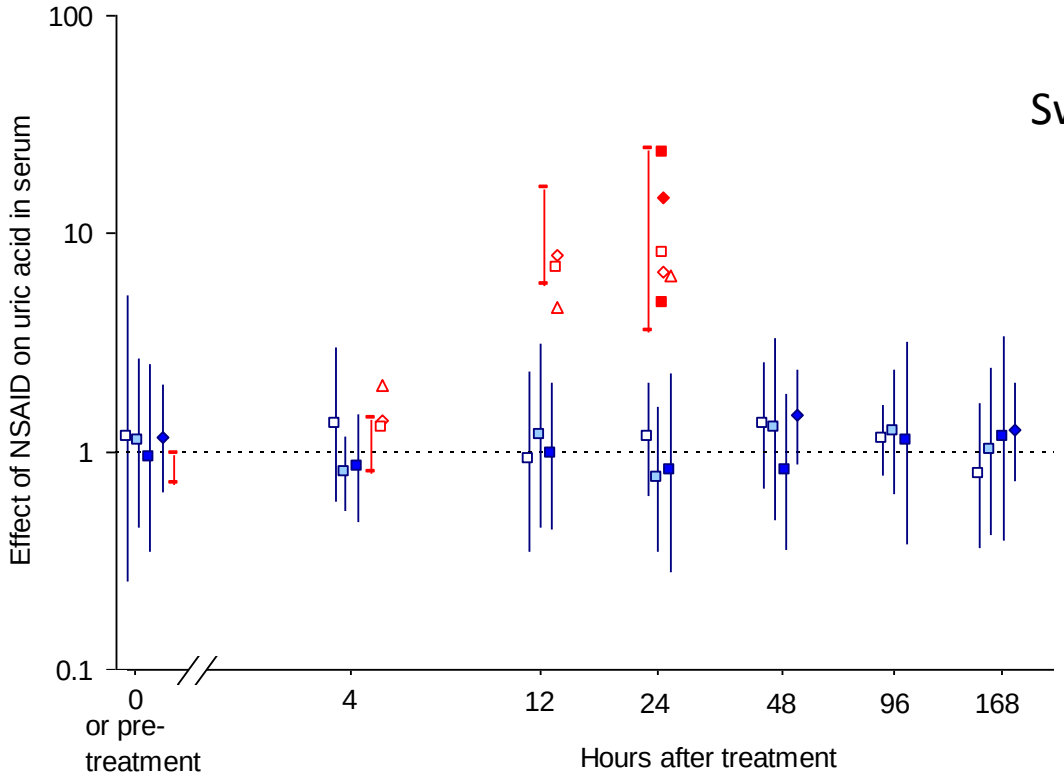
- Meloxicam safety tests in *Gyps* vultures in South Africa and India
  - Swan et al 2006b, Swarup et al. 2007

- Asian white-backed vulture *Gyps bengalensis,* African white-backed vulture *Gyps fulvus* and long-billed vultures *Gyps indicus*
- The maximum level of exposure (MLE) to meloxicam for an Asian white-backed vulture is 1.83 mg/kg body weight (bw)

- Doses above the MLE (2.0 mg/kg bw) did not kill 45 out of 45 vultures
- Doses below the MLE (0.5-1.0 mg/kg bw) did not kill 10 out of 10 vultures
- Residues in buffalo liver & muscle tissues (<0.01-2.45 mg/kg bw) did not kill 31 out of 31 vultures; and 20 out of 20 other species of scavenging bird

- *Meloxicam is not toxic to* Gyps *vultures at doses above the MLE*

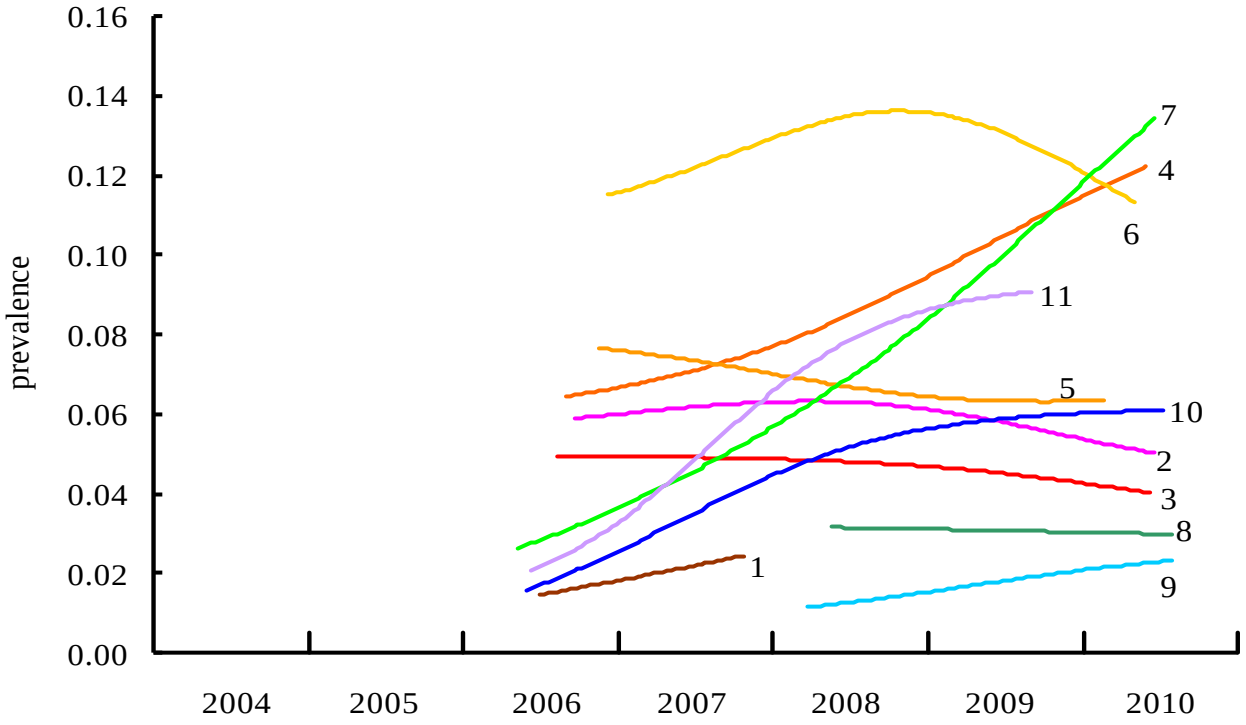
Meloxicam: Experimental evidence

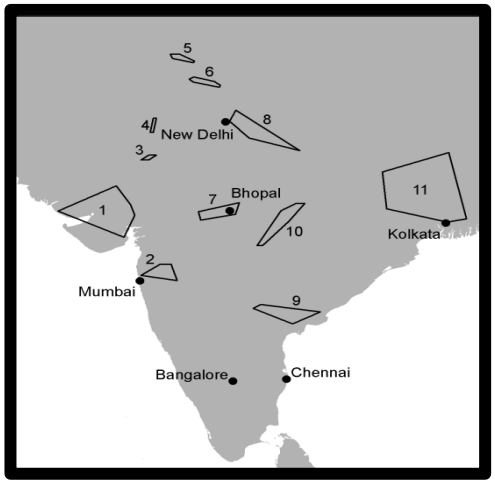


Swan et al. 2006b

- Serum uric acid increases ten times the normal level in *Gyps* vultures treated with diclofenac (red symbols)
- But is not increased at all in *Gyps* vultures treated meloxicam (blue symbols: low to high dose left to right of each group)

Meloxicam: field evidence





Cuthbert et al. 2014

- Repeated surveys of cattle carcasses in carcass dumps in India
- Proportion of carcasses with meloxicam residue is high and increasing in many regions surveyed

Meloxicam
Field evidence (I)

- Meloxicam in livers of cattle from the safety test
  - Average concentration = 8.5 mg/kg
- Meloxicam in livers of cattle from carcass surveys in India
  - Taggart et al. 2009
  - Average concentration = 0.3 mg/kg => 0.04 times that above
  - Maximum concentration = 1.7 mg/kg => 0.2 times that above
- MLE used in safety test is far greater than MLE found in cattle carcasses

- *MLE to meloxicam used in the safety test was at an appropriate level*

Meloxicam
Field evidence (II)

- Examination of wild *Gyps* vultures found dead in India (2005-2011)
  - Cuthbert et al. 2015
- Post mortem and tissue analysis for nine NSAIDs (n = 24)
  - 16 vultures (67%) had visceral gout
  - 1 vulture (4%) tested positive for meloxicam, but did not have vis. gout
    - Probably died for a reason not connected with NSAIDs
  - 1 vulture (4%) tested positive for meloxicam & nimesulide and had vis. gout
    - But 3 other vultures (13%) with vis. gout were positive for nimesulide and no other NSAID
    - Probably this vulture died from nimesulide, not meloxicam
- *Meloxicam is not killing* Gyps *vultures in the wild*

Meloxicam
Summary of evidence

- Safety testing has shown meloxicam at doses up to and above the MLE does not kill *Gyps* vultures or elevate their blood uric acid level
- The proportion of cattle carcasses available to *Gyps* vultures contain meloxicam is high and increasing
- Post mortem examination of wild *Gyps* vultures found dead in the field rarely have meloxicam residue and never meloxicam residue alone in association with visceral gout
- No cases of death in vultures and other birds following therapeutic use of meloxicam
- Therefore, wild *Gyps* vultures are exposed to meloxicam in domesticated ungulate carcasses where this drug is used for veterinary purposes in South Asia, but at non-lethal concentrations

Ketoprofen

Vulture-toxic drug #2

Presented by
Prof. Rhys Green,
Professor of Conservation Science,
RSPB Centre for Conservation Science
& University of Cambridge, UK

Ketoprofen
Clinical evidence

- Questionnaire on NSAID use and outcome in birds at zoos and wildlife centres worldwide
  - Cuthbert et al. 2007

- Ketoprofen caused no mortality in 3 out of 3 cases involving *Gyps* vultures
- Ketoprofen + carprofen caused visceral gout and death in 1 out of 1 case involving a *Gyps* vulture
- Ketoprofen + flunixin caused visceral gout and death in 1 out of 1 case involving a *Gyps* vulture

- *Ketoprofen toxicity is unclear*

Ketoprofen
Experimental evidence (I)

- Ketoprofen Safety test in African *Gyps* vultures
  - Naidoo et al. (2009)

- The Cape griffon vulture *G. coprotheres* is of a similar size to the Himalayan griffon vulture *G. himalayensis*
- The maximum level of exposure (MLE) to ketoprofen for a Himalayan griffon vulture is 1.16 mg/kg body weight

- Ketoprofen at doses above the MLE (5 mg/kg bw) killed 7 out of 11 Cape griffon vultures
  - elevated uric acid concentrations in plasma
  - kidney damage and visceral gout

- *Ketoprofen is toxic to* Gyps *vultures at a dose above the MLE*

Ketoprofen
Experimental evidence (II)

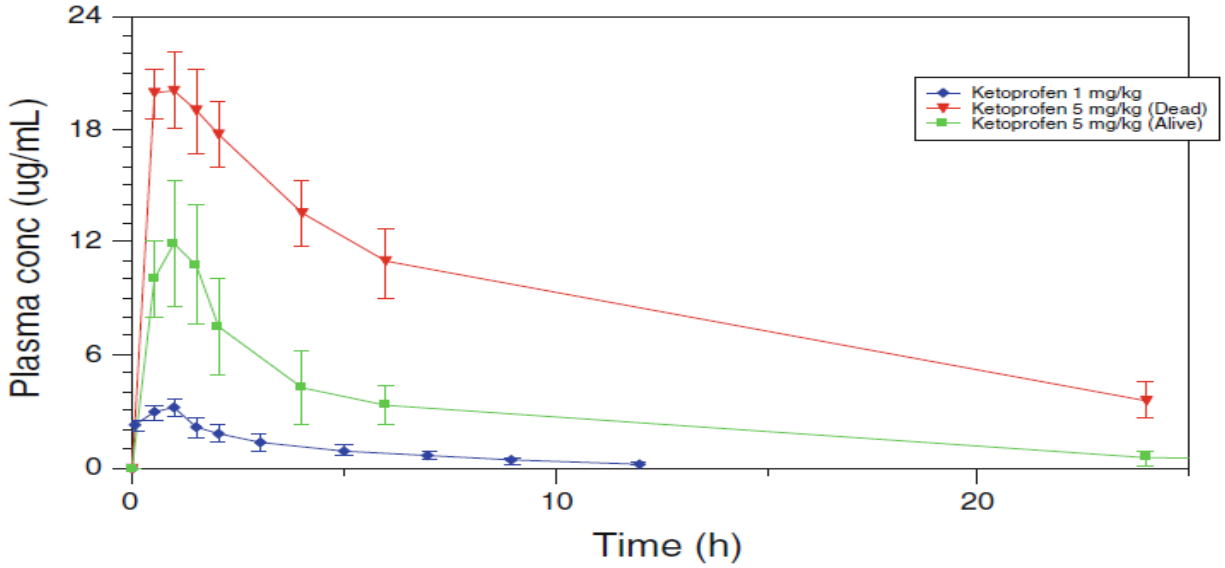
- Another ketoprofen safety test in African *Gyps* vultures
  - Naidoo et al (2007)

- The African white-backed vulture *G. africanus* is of a similar size to the Asian white-backed vulture *G. bengalensis*
- The maximum level of exposure (MLE) to ketoprofen for an Asian white-backed vulture is 1.54 mg/kg body weight

- Ketoprofen at a dose below the MLE (1.5 mg/kg bw) killed 1 out of 11 African white-backed vulture
  - elevated uric acid concentrations in plasma
  - Kidney damage and visceral gout

- *Ketoprofen is toxic to* Gyps *vultures at a dose below the MLE*

Ketoprofen: experimental evidence



Naidoo et al. (2009)

- Plasma concentration versus time profile for the Cape griffon vultures exposed to ketoprofen at
  - 1 mg/kg bw & survived (blue)
  - 5 mg/kg bw & survived (green)
  - 5 mg/kg bw & died (red)
- Vultures that died absorbed more and eliminated less than those that survived over the same period

Ketoprofen
Field evidence

- Ketoprofen in livers of cattle from the safety test
  - Average concentration = 0.16 mg/kg

- Ketoprofen in livers of cattle from carcass surveys in India
  - Taggart et al. (2009)
  - Average concentration = 0.4 mg/kg => 2.5 times that above
  - Maximum concentration = 5.6 mg/kg => 35 times that above

- Ketoprofen overdosing in animals close to death

Ketoprofen
Field evidence

- Average concentration of ketoprofen from safety test
  - Liver = 0.16 mg/kg
  - Kidney = 7.13 mg/kg => 44.5 times that in liver
- Kidney not sampled in the field, but if we assume the
  - Average conc. is 2.5 times that in kidney above
  - Maximum conc. is 35 times that in kidney above
- MLE of ketoprofen
  - Kidney (average conc. from the field) = 3.83 mg/kg bw
  - Kidney (maximum conc. from the field) = 53.59 mg/kg bw
- *The actual MLE of ketoprofen to* Gyps *vultures is greater than that used in safety testing*

Ketoprofen
Summary of evidence

- Safety testing shows ketoprofen at doses below and above the MLE can kill *Gyps* vultures

- Survey of NSAIDs concentrations in domesticated ungulate carcasses reveals that the actual MLE of ketoprofen is greater than that calculated for safety testing because NSAID-users regularly overdose animals close to death

- Therefore, wild *Gyps* vultures are exposed to lethal concentrations of ketoprofen in domesticated ungulate carcasses where this drug is used for veterinary purposes in South Asia

Flunixin & Nimesulide

Vulture-toxic drug #3 & #4

Presented by
Dr. Mohini Saini,
Principal Scientist,
ICAR-IVRI, India

Flunixin
Clinical evidence

- Questionnaire on NSAID use and outcome in birds at zoos and wildlife centres worldwide
  - Cuthbert et al. (2007)

- Flunixin caused visceral gout and death in
  - 2 out of 4 cases involving *Gyps* vultures
  - 6 out of 20 cases involving other birds, including scavenging raptors
- Flunixin + ketoprofen caused visceral gout and death in 1 out of 1 case involving a *Gyps* vulture

- *Flunixin appears to be toxic to* Gyps *vultures*

Flunixin
Experimental evidence

- Flunixin safety test in African *Gyps* vultures
  - Fourie et al. (2015)

- The Cape griffon vulture *G. coprotheres* is of a similar size to the Himalayan griffon vulture *G. himalayensis*
- The maximum level of exposure (MLE) to flunixin for a Himalayan griffon vulture is 0.32 mg/kg body weight (predicted from Fourie et al. (2015))

- Flunixin at a dose above the MLE (1 mg/kg bw) did not kill 2 Cape griffon vultures

Flunixin
Experimental evidence

- But
  - Symptoms of toxicity (e.g. lethargy and depression)
  - Elevated alanine transferase (ALT) concentrations
  - Elevated uric acid concentrations in plasma
  - Only two vultures were tested (cf. meloxicam n = 45)

- *Flunixin appears to be toxic to* Gyps *vultures; sample size too small to say it is not toxic*

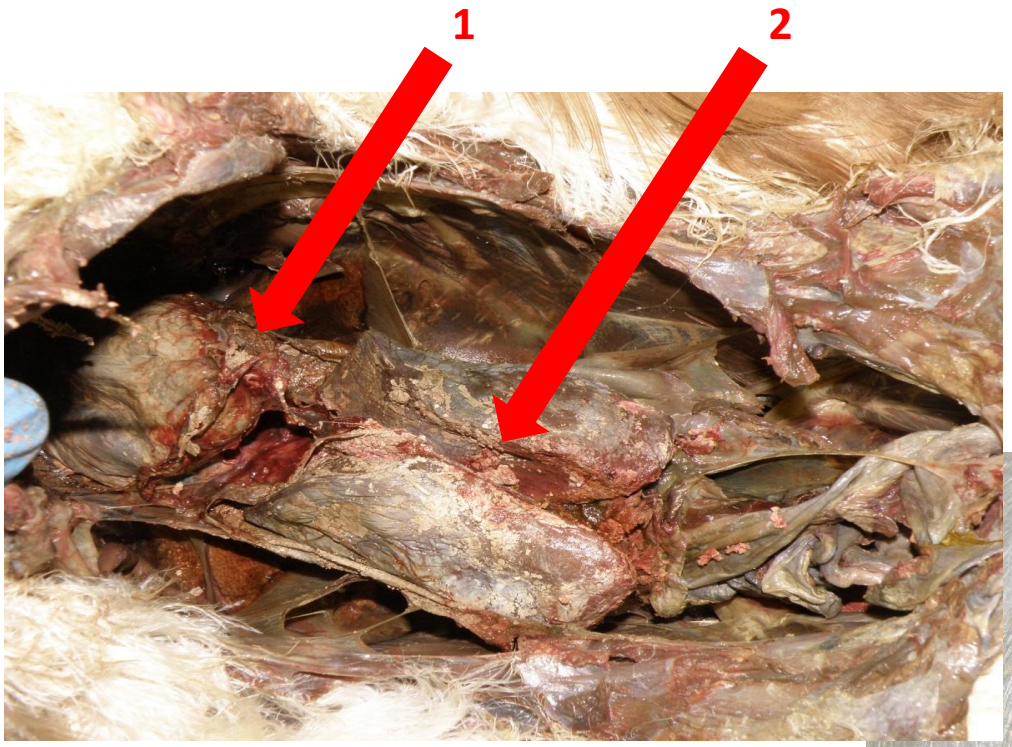
Flunixin
Field evidence

- Post mortem examination of wild *Gyps* vultures found dead in Spain
  - Zorrilla et al. (2014), one case
  - Spanish Wildlife Authorities (unpublished), four cases

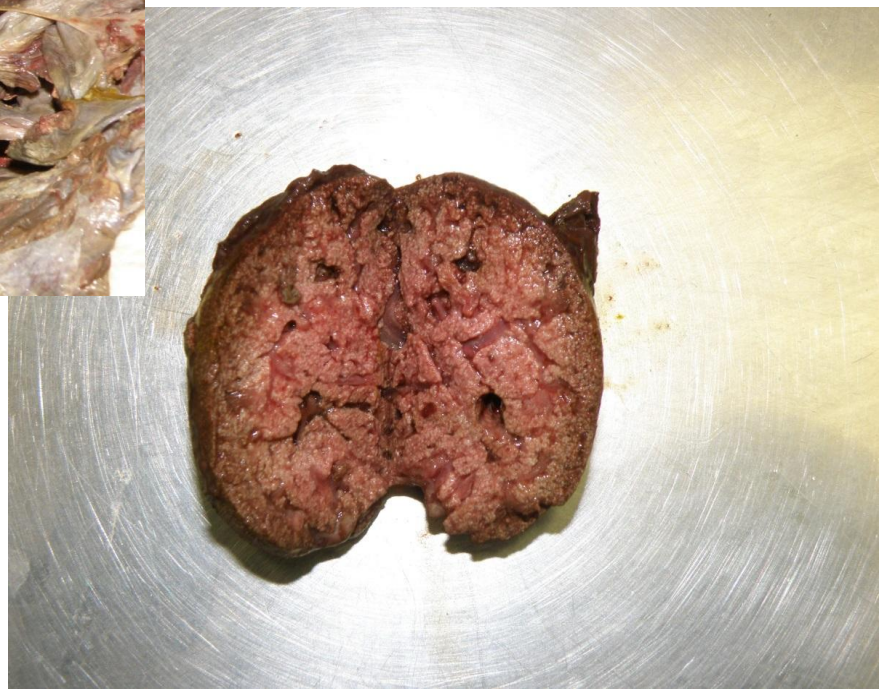
- Five vultures tested positive for flunixin and negative for diclofenac
- All five showed visceral gout

- *As with diclofenac, flunixin is associated with visceral gout in dead* Gyps *vultures; therefore, flunixin is probably killing* Gyps *vultures in the wild*

Flunixin: Field evidence



Zorrilla et al. (2014)



Nimesulide
Clinical & experimental evidence

- At present, there is no clinical and experimental data for nimesulide

Nimesulide
Field evidence

- Post mortem examination of wild *Gyps* vultures found dead in India
  - Cuthbert et al. 2015

- Five vultures tested positive for nimesulide and negative for diclofenac
- Four of these had visceral gout
- The one without visceral gout had a very low level of nimesulide

- One of the four above was also positive for meloxicam
- But meloxicam at a high concentration was not associated with visceral gout in a sixth vulture

- *As for diclofenac, nimesulide is associated with visceral gout in dead* Gyps *vultures; nimesulide is probably killing* Gyps *vultures in the wild*

Flunixin & Nimesulide summary of evidence

- Post mortem examination of wild *Gyps* vultures found dead in the field have shown both flunixin and nimesulide residues in association with visceral gout, even though these individuals were negative for diclofenac
- Because diclofenac causes visceral gout and death in *Gyps* vultures, it is logical to expect that nimesulide and flunixin cause visceral gout and death as well
- Clinical and experimental evidence provide some support for the toxicity of flunixin to *Gyps* vultures
- Therefore, wild *Gyps* vultures are probably exposed to lethal concentrations of flunixin and nimesulide in domesticated ungulate carcasses where these drugs are used for veterinary purposes in South Asia

Aceclofenac

Vulture-toxic drug #5

Presented by
Nic Masters,
Head, Veterinary Services,
ZSL, UK

Aceclofenac: Experimental evidence

- Pharmacokinetics study in cattle *Bos taurus* in South Africa
  - Galligan et al. (2015)

- Indian recommended dose given and blood sampled (0-12h)
  - At 0.25h, diclofenac is detected
  - At 2.0h, 50% of the aceclofenac had converted to diclofenac
  - At 12.0h, 80% of the aceclofenac had converted to diclofenac

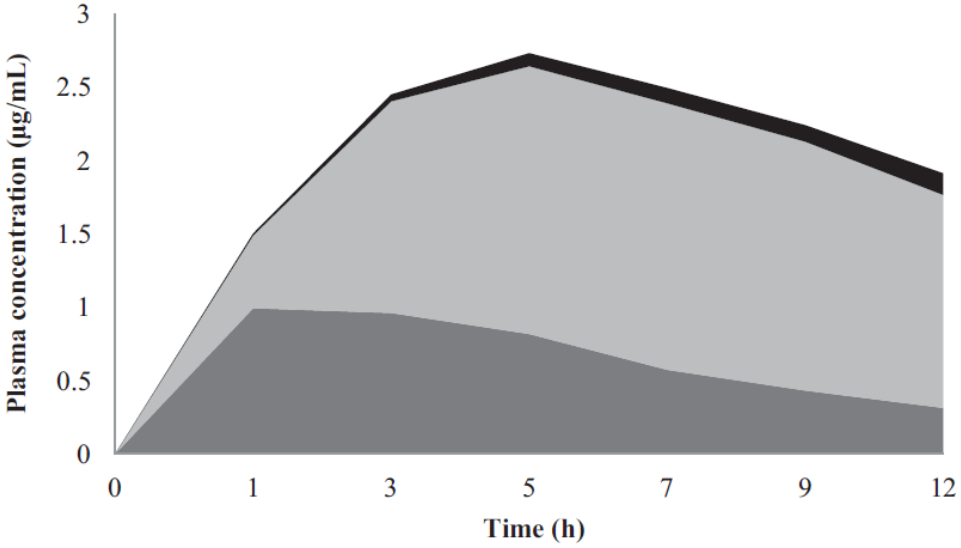


Figure 3. Additive geometric mean plasma concentration over time for aceclofenac (dark gray), diclofenac metabolite of aceclofenac (light gray), and 4'-hydroxydiclofenac metabolite of aceclofenac (black) in 6 female Bos taurus cattle.

Aceclofenac
Experimental evidence

- Almost all aceclofenac is converted into diclofenac in cattle plasma
- Kinetic homogeneity
  - Absorption & elimination profiles are similar in all tissues

- Therefore, aceclofenac is a pro-drug of diclofenac
- And aceclofenac products poses a similar threat to *Gyps* vultures as diclofenac products
- Safety testing in *Gyps* vultures is unnecessary

- *Aceclofenac converts to diclofenac – a known vulture-toxic NSAID*

Aceclofenac
Summary of evidence

- An experiment study has shown that a very high proportion of aceclofenac administered to cattle is quickly converted into diclofenac

- Therefore, wild *Gyps* vultures are exposed to lethal concentrations of diclofenac in domesticated ungulate carcasses where aceclofenac is used for veterinary purposes in South Asia

- In fact, some dead vultures that we find with diclofenac residue may have consume tissue from carcasses of domesticated ungulates treated with aceclofenac

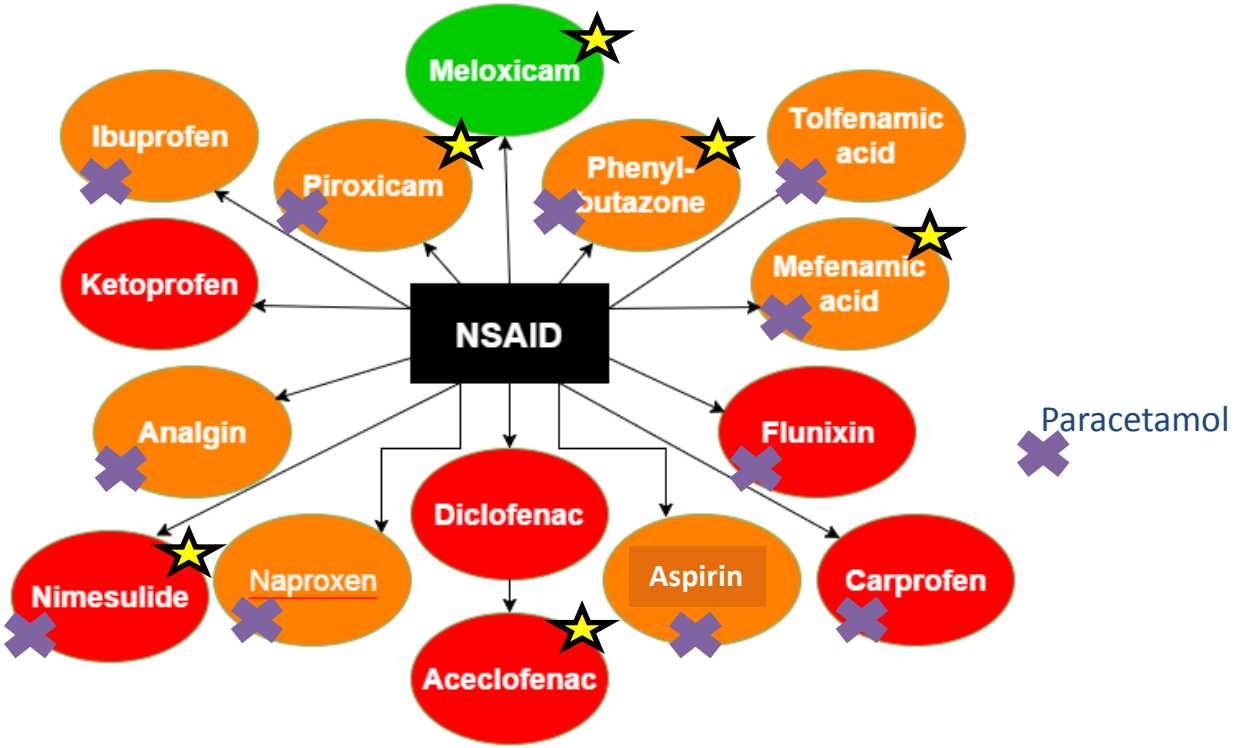
Future NSAID safety tests

Looking for vulture-toxic & vulture-safe NSAIDs

Present by
Dr. Toby Galligan,
Senior Conservation Scientist,
RSPB Centre for Conservation, UK

Other NSAIDs in South Asia

- Fifteen NSAIDs are used as veterinary treatments throughout South Asia



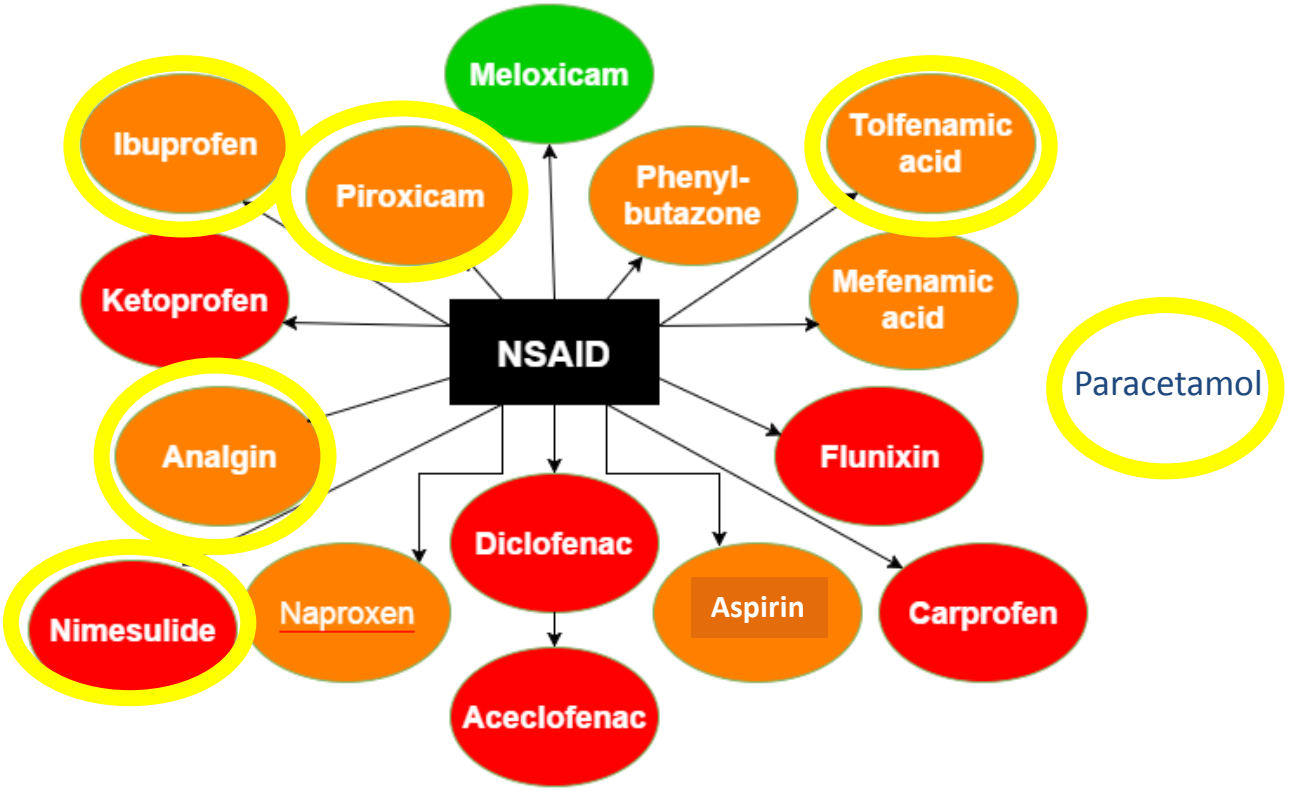
Paracetamol is often combined with some NSAIDs, including meloxicam

Sixteen drugs have not been thoroughly safety tested in *Gyps* vultures

- Some may be vulture-safe, other will be vulture-toxic

Current safety testing project

- BNHS and IVRI project supported by SAVE
- Funded by MoEF and Haryana Government
- Safety test for 6 out of 8 NSAIDs that need to be tested



Current safety testing project

- Aim: determine vulture-safe and vulture-toxic NSAIDs
- Timeframe: 3-6 years

- Each safety test will be a multiple-phase controlled experiment
  - Find maximum residue levels in buffalo tissues for the MLE
  - Expose *Gyps* vultures to oral doses at MLE and tissue feeds from treated buffalo at double the recommended dose
  - Minimal vultures at risk of death by exposing vultures in stages
  - Use Himalayan griffon vultures *G. himalayensis* (NT) and Asian white-backed vultures *G. bengalensis* (CE)
  - Test ends when toxicity is clearly shown in each species
  - Or toxicity is very unlikely (i.e., no evidence of toxicity in a large sample of vultures)

Veterinary NSAIDs in Bangladesh

Presented by
Prof. Monirul Khan,
Department of Zoology,
Jahangirnagar University,
Bangladesh

Diclofenac, ketoprofen & meloxicam

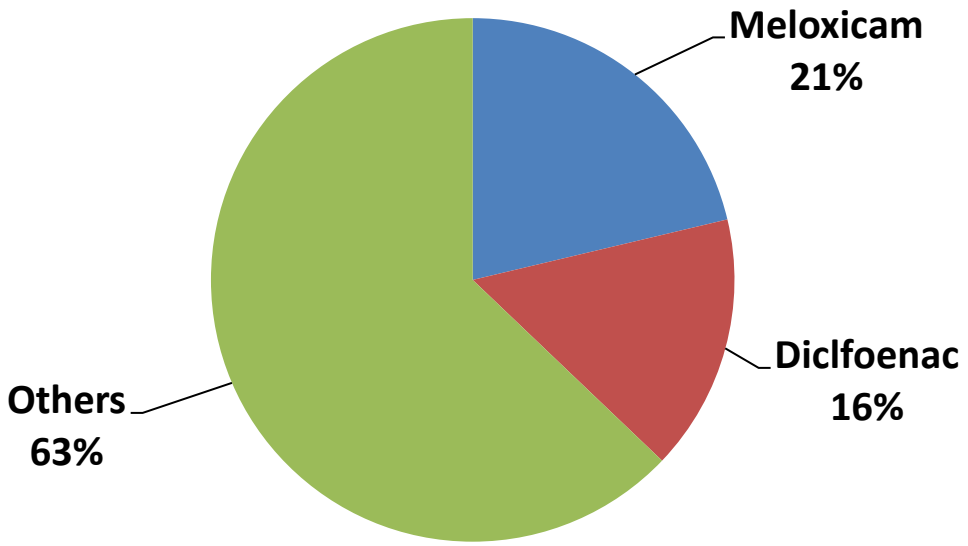
- Production, sale and use of veterinary diclofenac banned in 2010
- Meloxicam promoted as a vulture-safe alternative by
  - Government
  - Medicine companies
- Use of veterinary ketoprofen banned in 2015 in Bangladesh's two provisional Vulture Safe Zones

Veterinary NSAIDs in Bangladesh

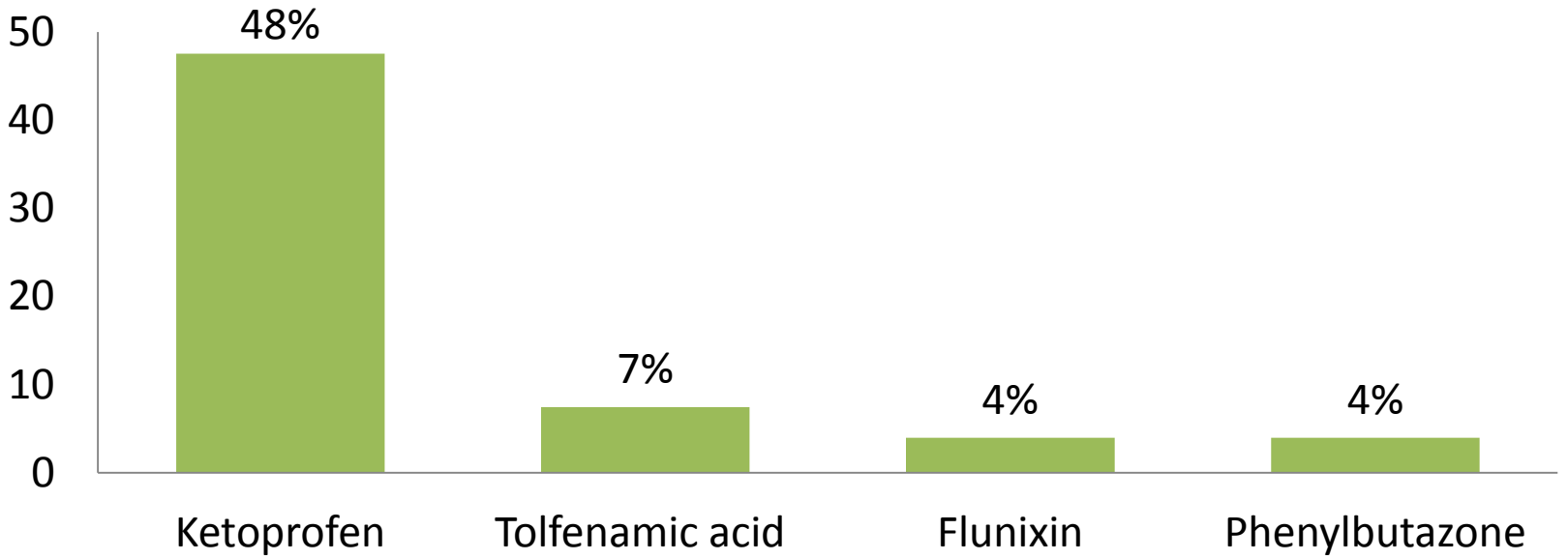
- Undercover pharmacy surveys
  - 2014 and 2016
  - Two provisional Vulture Safe Zones
  - Undercover surveyor asks pharmacists for “a painkiller for their injured cow”
  - Data is from 1 item per pharmacy per settlement per year
  - 470 data points

Veterinary NSAIDs in Bangladesh

- 21% of NSAIDs were meloxicam
- 16% of NSAIDs were diclofenac – made in Bangladesh and India
- The remaining 63% were other NSAIDs
  - Nearly half of all NSAIDs were ketoprofen



Veterinary NSAIDs in Bangladesh



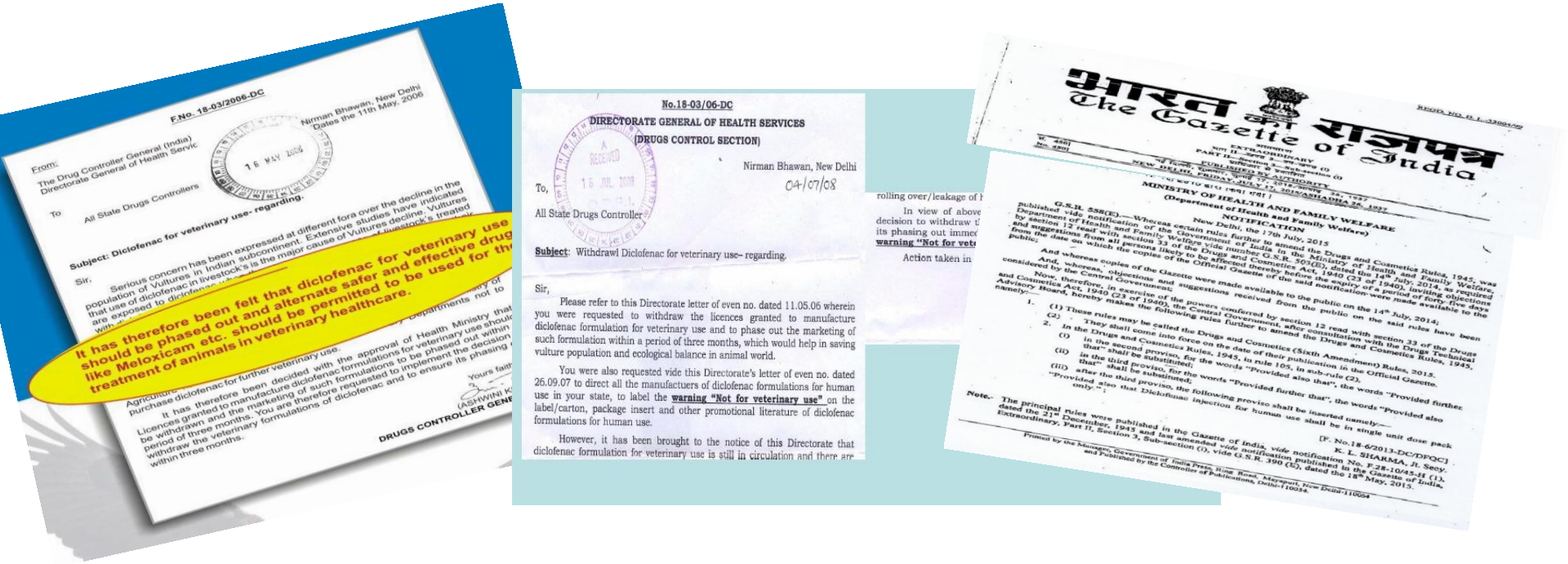
- Four other NSAIDs were found
- Two that are toxic to *Gyps* vultures:
  - ketoprofen certainly; flunixin probably
- Two of unknown toxicity to *Gyps* vultures:
  - Phenylbutazone and tolfenamic acid

Veterinary NSAIDs in India

Presented by
Dr. Parag Deori,
Head Veterinarian,
BNHS, India

Diclofenac ban & meloxicam promotion

- Manufacture, distribution & sale of veterinary diclofenac banned in 2006
  - Notification in gazette in 2008
- Meloxicam promoted as a vulture-safe alternative by government
- Manufacture of human diclofenac restricted to single dose vials
  - Notification in gazette in 2015

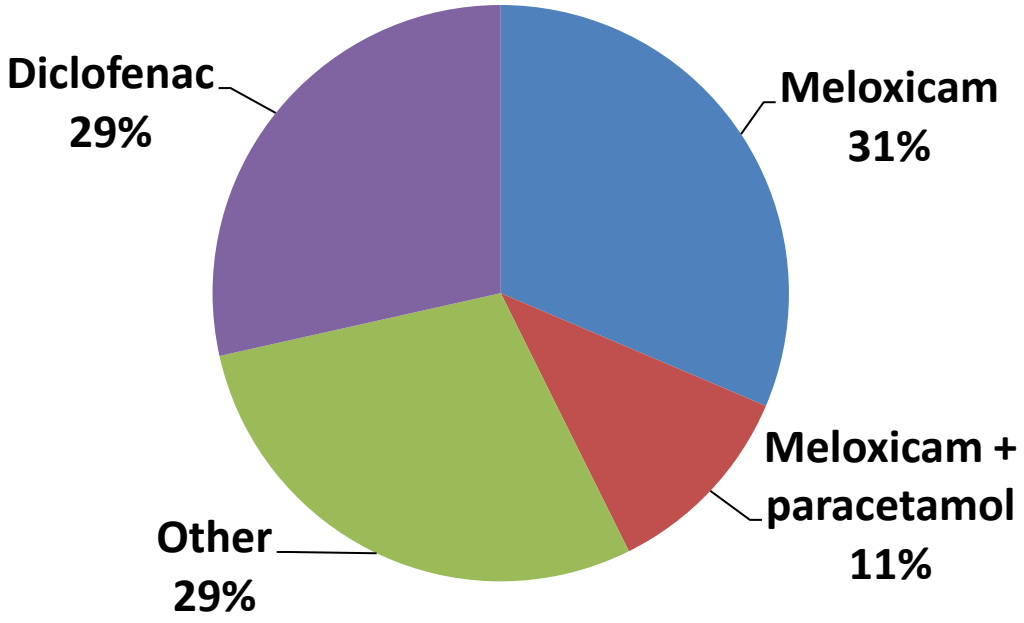


Veterinary NSAIDs in India

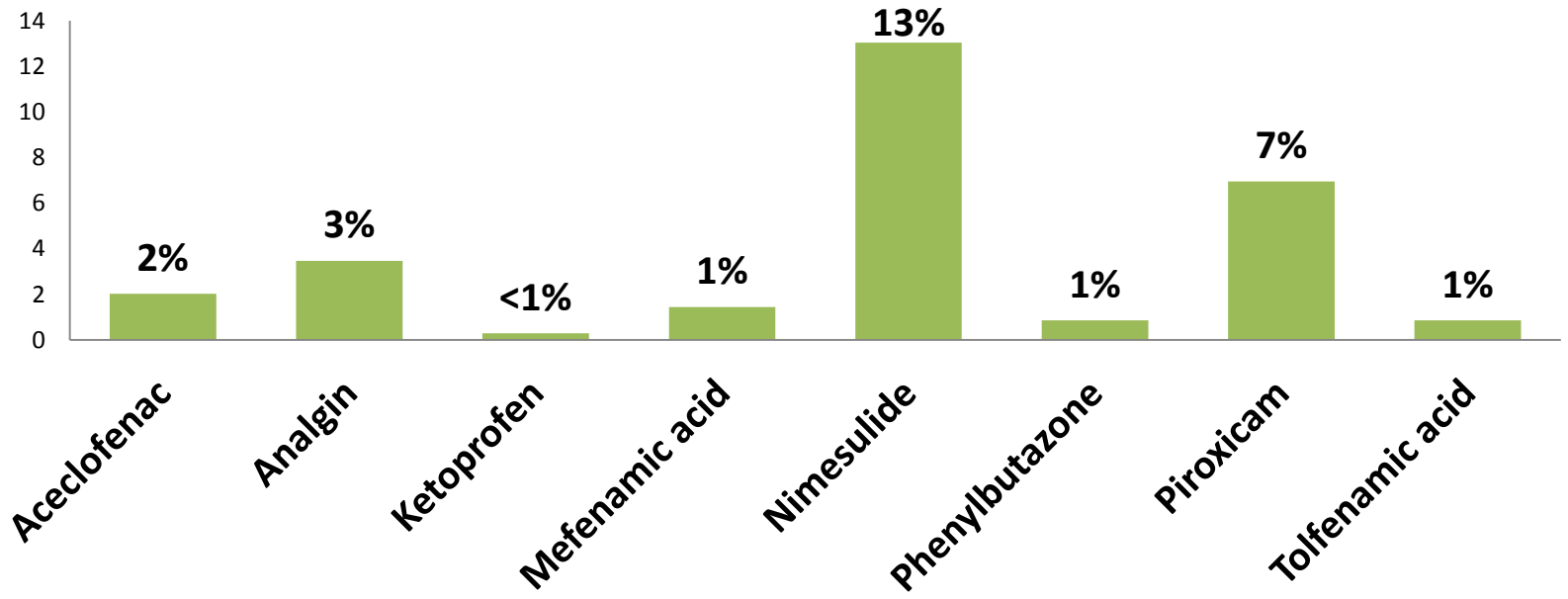
- Undercover pharmacy surveys
  - 2012-2015 (before MDVD ban [mid-2015])
  - Assam, Gujarat, Jharkhand, Uttar Pradesh and Uttarakhand
  - Undercover surveyor asks pharmacists for “a painkiller for their injured cow”
  - Data is from 1 item per pharmacy per settlement
  - 638 data points
- Open surveys were also conducted; and showed similar results to undercover surveys

Veterinary NSAIDs in India

- One third of sales were either
  - Meloxicam
  - Diclofenac – hence the MDVD ban
  - Other NSAIDs combined
- The remaining 10% of sales were meloxicam with paracetamol



Veterinary NSAIDs in India



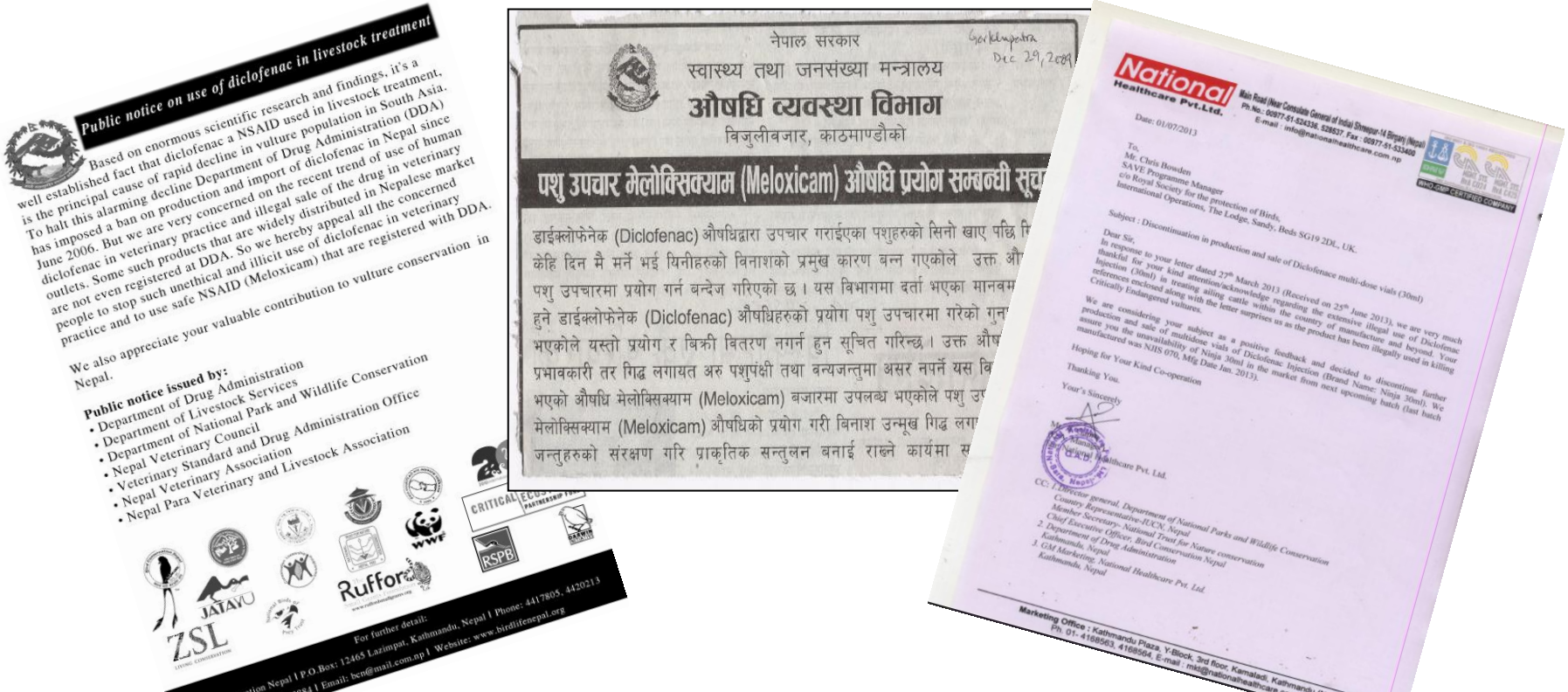
- Eight other NSAIDs were found
- Three that are toxic to *Gyps* vultures:
  - aceclofenac & ketoprofen certainly; nimesulide probably
- Five of unknown safety to *Gyps* vultures:
  - analgin, mefenamic acid, phenylbutazone, piroxicam and tolfenamic acid

Veterinary NSAIDs in Nepal

Presented by
Laxman P. Poudyal,
Ecologist,
Department of National Park and Wildlife Conservation, Nepal

Diclofenac ban & meloxicam promotion

- Manufacture & importation of veterinary diclofenac banned in 2006
- Meloxicam promoted as a vulture-safe alternative by government
- One Nepalese company began manufacturing human diclofenac in multiple-dose vials, but voluntarily discontinued manufacture following letter from SAVE



Public notice on use of diclofenac in livestock treatment

Based on enormous scientific research and findings, it's a well established fact that diclofenac a NSAID used in livestock treatment, is the principal cause of rapid decline in vulture population in South Asia. To halt this alarming decline Department of Drug Administration (DDA) has imposed a ban on production and import of diclofenac in Nepal since June 2006. But we are very concerned on the recent trend of use of human diclofenac in veterinary practice and illegal sale of the drug in veterinary outlets. Some such products that are widely distributed in Nepalese market are not even registered at DDA. So we hereby appeal all the concerned people to stop such unethical and illicit use of diclofenac in veterinary practice and to use safe NSAID (Meloxicam) that are registered with DDA.

We also appreciate your valuable contribution to vulture conservation in Nepal.

Public notice issued by:
- Department of Drug Administration
- Department of Livestock Services
- Department of National Park and Wildlife Conservation
- Nepal Veterinary Council
- Veterinary Standard and Drug Administration Office
- Nepal Veterinary Association
- Nepal Para Veterinary and Livestock Association

नेपाल सरकार
स्वास्थ्य तथा जनसंख्या मन्त्रालय
औषधि व्यवस्था विभाग
विजुलीबजार, काठमाण्डौको

Gorkhapatra Dec 29, 2009

पशु उपचार मेलोक्सिक्याम (Meloxicam) औषधि प्रयोग सम्बन्धी सूच

डाईक्लोफेनेक (Diclofenac) औषधिद्वारा उपचार गराईएका पशुहरुको सिनो खाए पछि नि
केहि दिन मै मर्ने भई यिनीहरुको विनाशको प्रमुख कारण बन्न गएकोले उक्त औ
पशु उपचारमा प्रयोग गर्न बन्देज गरिएको छ । यस विभागमा दर्ता भएका मानवम
हुने डाईक्लोफेनेक (Diclofenac) औषधिहरुको प्रयोग पशु उपचारमा गरेको गुन
भएकोले यस्तो प्रयोग र बिक्री वितरण नगर्न हुन सूचित गरिन्छ । उक्त औष
प्रभावकारी तर गिद्ध लगायत अरु पशुपंक्षी तथा वन्यजन्तुमा असर नपर्ने यस वि
भएको औषधि मेलोक्सिक्याम (Meloxicam) बजारमा उपलब्ध भएकोले पशु उ
मेलोक्सिक्याम (Meloxicam) औषधिको प्रयोग गरी विनाश उन्मुख गिद्ध लगा
जन्तुहरुको संरक्षण गरि प्राकृतिक सन्तुलन बनाई राख्ने कार्यमा स

National Healthcare Pvt.Ltd.
Main Road (Near Consulate General of Indian) Shreepur-14 Birgunj (Nepal)
Ph.No.: 00977-51-524336, 528637, Fax : 00977-51-533409
E-mail : info@nationalhealthcare.com.np

Date: 01/07/2013

To,
Mr. Chris Bowden
SAVE Programme Manager
c/o Royal Society for the protection of Birds,
International Operations, The Lodge, Sandy, Beds SG19 2DL, UK.

Subject : Discontinuation in production and sale of Diclofenace multi-dose vials (30ml)

Dear Sir,
In response to your letter dated 27th March 2013 (Received on 25th June 2013), we are very much thankful for your kind attention/acknowledge regarding the extensive illegal use of Diclofenac injection (30ml) in treating ailing cattle within the country of manufacture and beyond. Your references enclosed along with the letter surprises us as the product has been illegally used in killing Critically Endangered vultures.

We are considering your subject as a positive feedback and decided to discontinue further production and sale of multidose vials of Diclofenac Injection (Brand Name: Ninja 30ml). We assure you the unavailability of Ninja 30ml in the market from next upcoming batch (last batch manufactured was NHS 070, Mfg Date Jan. 2013).

Hoping for Your Kind Co-operation

Thanking You.

Your's Sincerely

Healthcare Pvt. Ltd.

CC: 1.Director general, Department of National Parks and Wildlife Conservation
Country Representative-IUCN, Nepal
Member Secretary-National Trust for Nature conservation
Chief Executive Officer, Bird Conservation Nepal
2. Department of Drug Administration
Kathmandu, Nepal
3. GM Marketing, National Healthcare Pvt. Ltd.
Kathmandu, Nepal

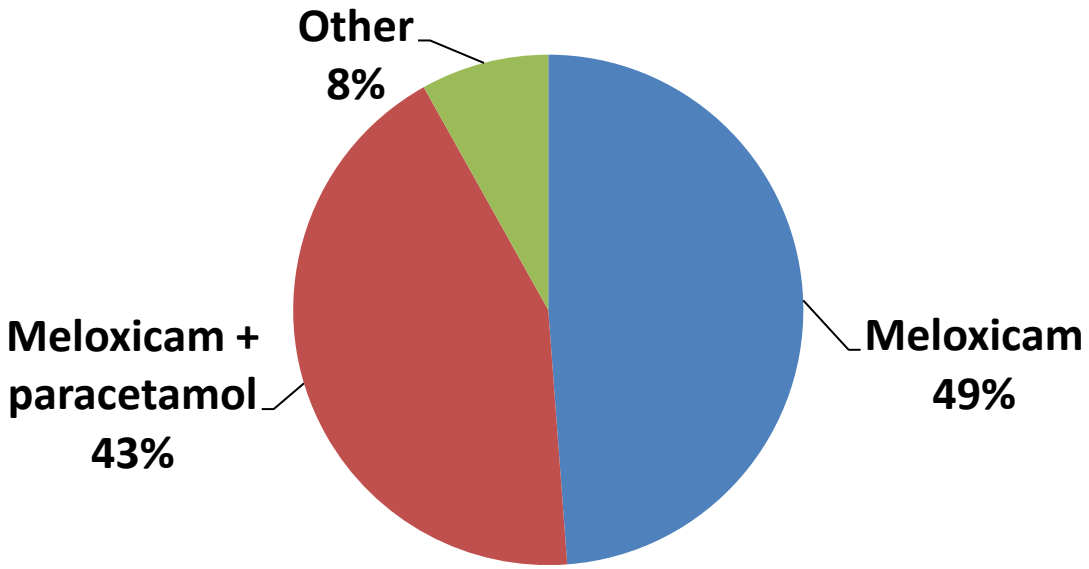
Marketing Office : Kathmandu Plaza, Y Block, 3rd floor, Kamaladi, Kathmandu

Veterinary NSAIDs in Nepal

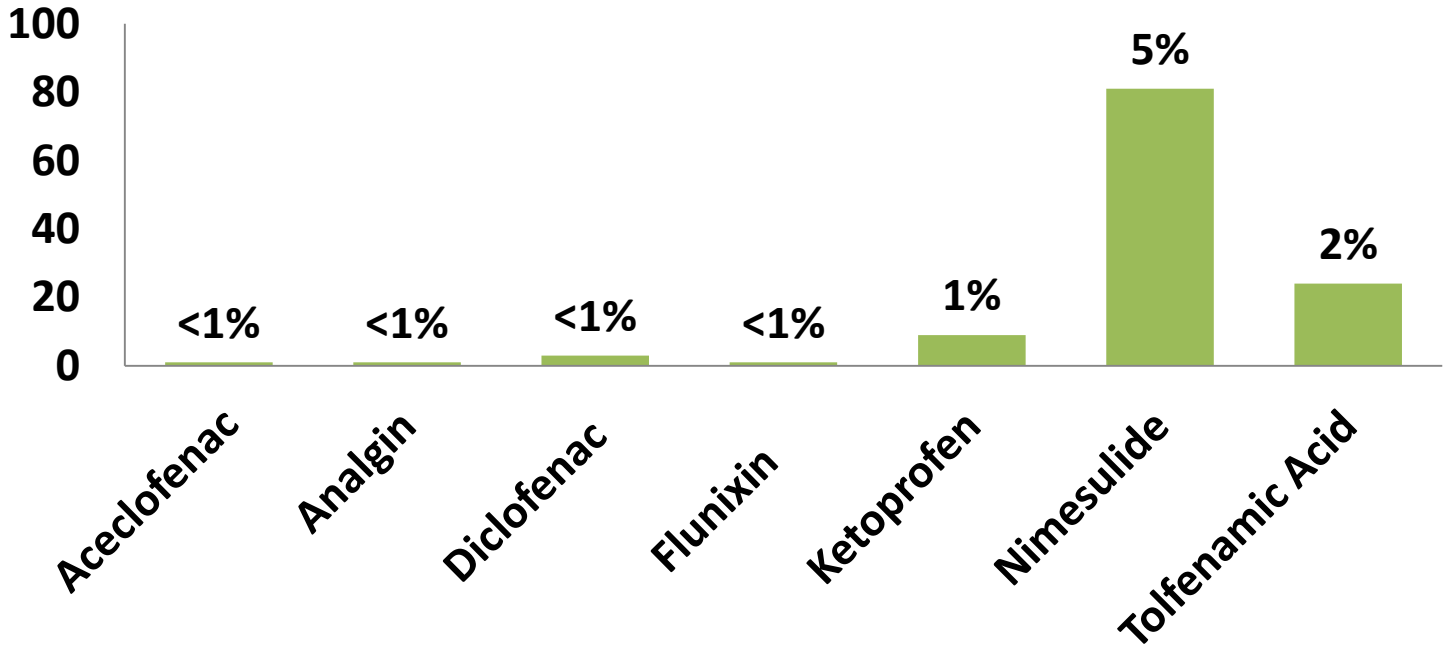
- Open veterinary pharmacy surveys
  - 2011-2016
  - Lowlands and mid-hills in Central, Western, Mid-Western and Far-Western DR, but not Eastern DR
  - Pharmacists asked to show all NSAIDs available for use in cattle and buffalo
  - Data comes from 1479 item found in 976 pharmacies
- Undercover surveys were also conducted; and showed similar results to open surveys

Veterinary NSAIDs in Nepal

- More than 90% of NSAIDs recorded were meloxicam
  - Most were made in Nepal
  - But nearly half were meloxicam with paracetamol
- Less than 10% were other NSAIDs
  - All of these were made in India



Veterinary NSAIDs in Nepal



- Seven other NSAIDs were found
- Five are toxic to *Gyps* vultures:
  - aceclofenac, diclofenac, & ketoprofen certainly
  - flunixin & nimesulide probably
- Two are of unknown toxicity to *Gyps* vultures
  - analgin & tolfenamic acid

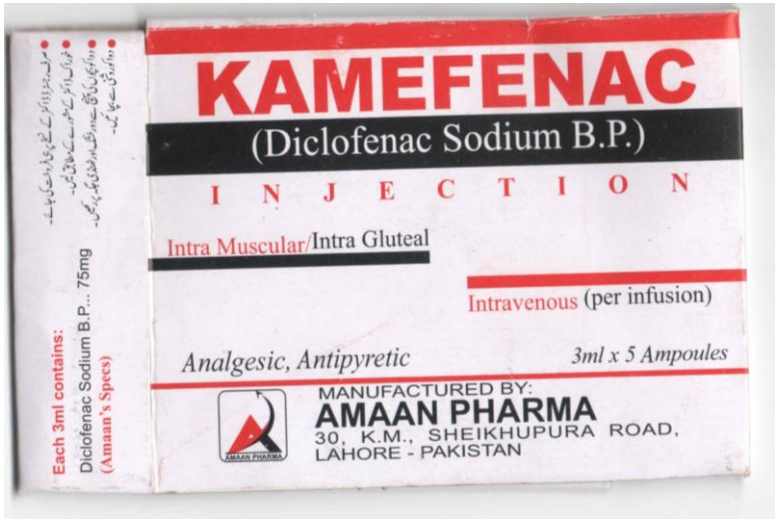
Veterinary NSAIDs in Pakistan

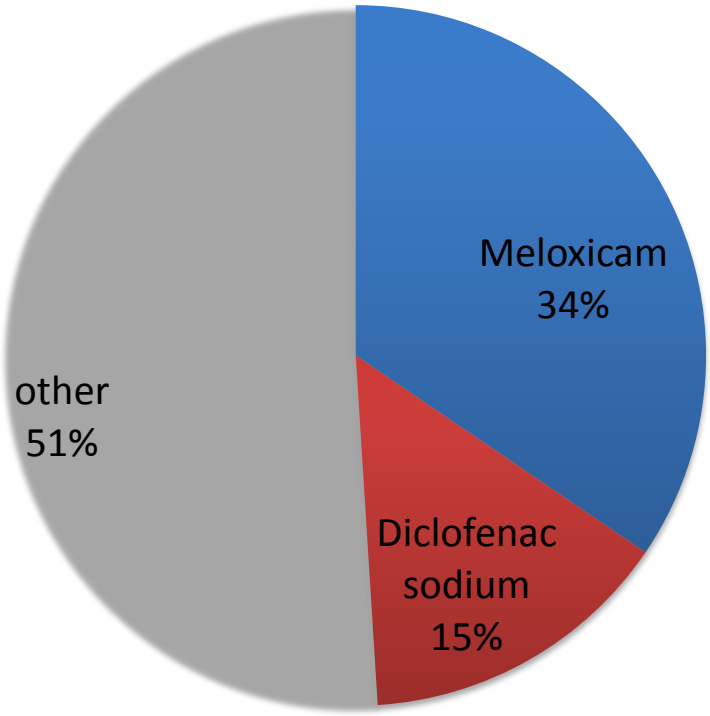
Presented by

Uzma Khan

Proportion of NSAIDs

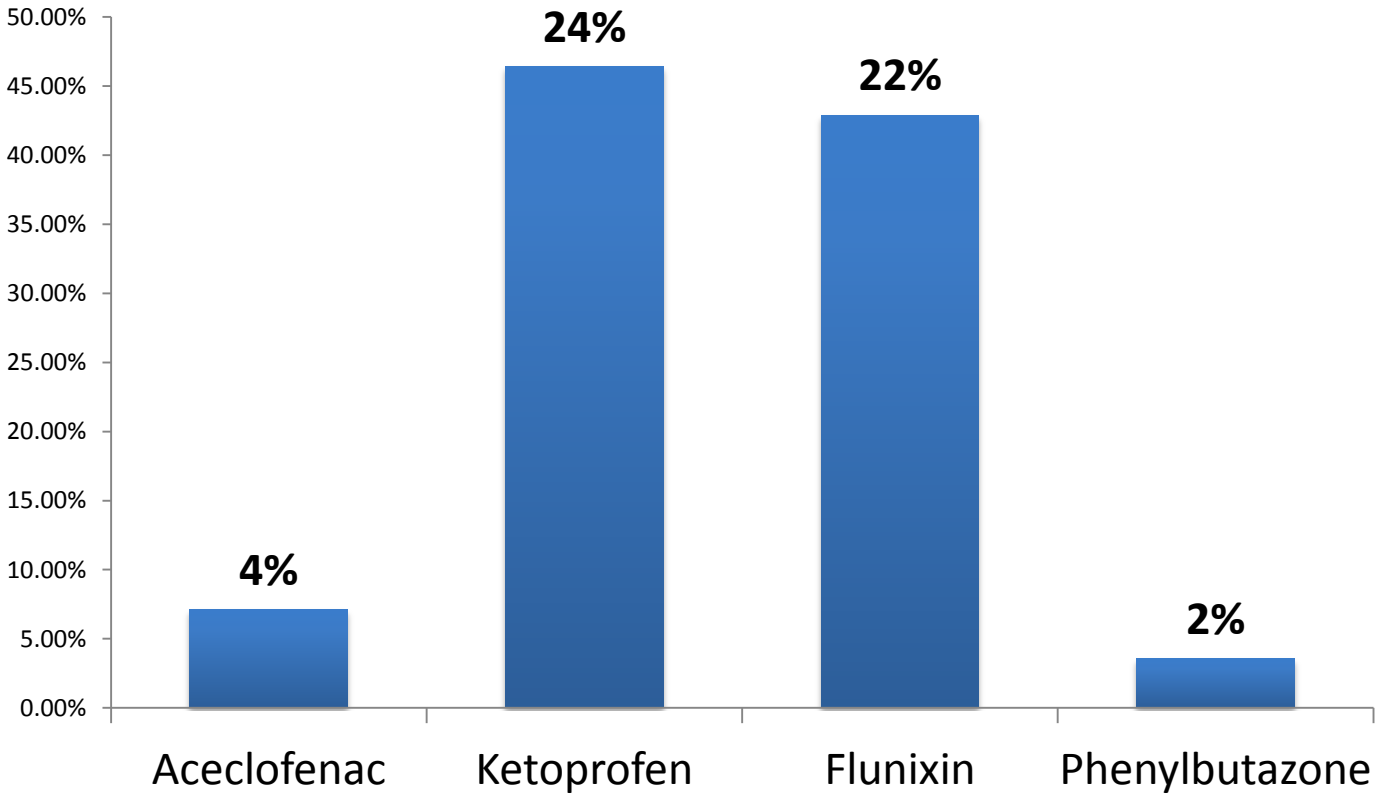
- Undercover survey results from 2015 and 2016 in three provinces; Punjab, (4) Sindh (13) and AJK (1)
- Results based on 55 samples collected 18 stores (including wholesalers/suppliers.
- Surveyors pretended to veterinary science students.



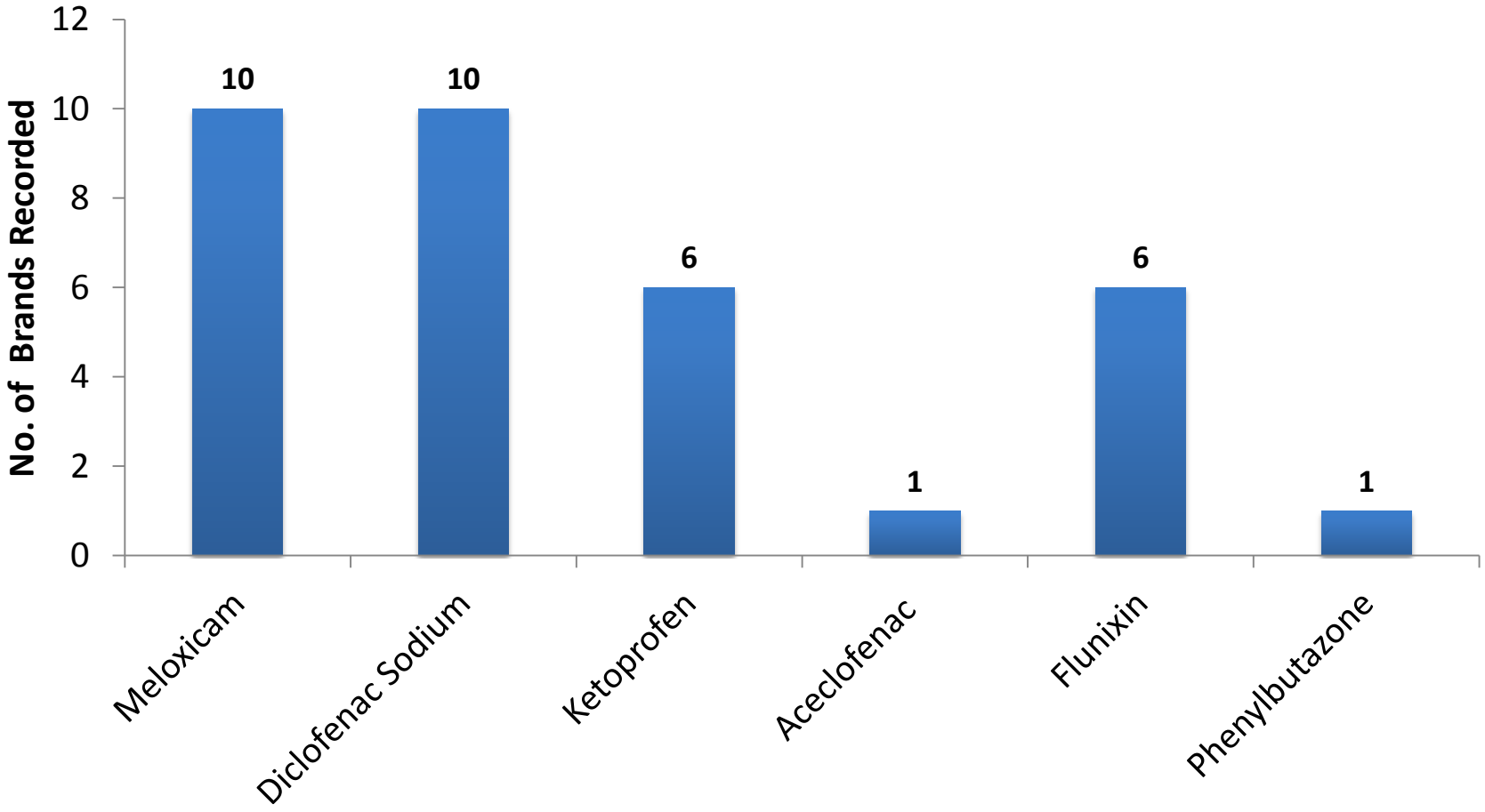


Veterinary NSAIDs in Pakistan

28 samples of ‘others’, dominated by ketoprofen and flunixin while aceclofenac was only found twice and phenylbutazone once



Veterinary NSAIDs in Pakistan

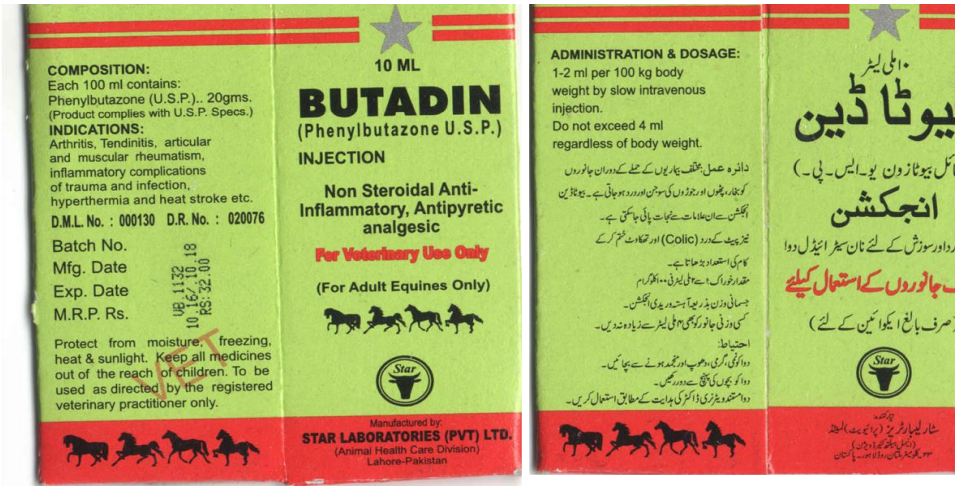


Veterinary NSAIDs in Pakistan

Only one veterinary store with one formulation of Phenylbutazone was found in Lahore – unknown toxicity?

Veterinary nimesulide was not found however it has been seen in medical stores.

Imported (Chinese) diclofenac sodium injections have also been seen in veterinary stores



NSAID Alert!

Summary &
effectiveness of meloxicam

Presented by
Prof. David Houston,
Chairman, SAVE &
University of Glasgow, UK

NSAIDs
Review of toxicity to *Gyps* vultures

NSAID	Causes death after experimental treatment at the MLE	Associated with visceral gout in dead vultures	Associated with death after therapeutic treatment
Diclofenac/Aceclofenac	☑	☑	☐
Meloxicam	☒	☒	☒
Ketoprofen	☑	☐	☐
Flunixin	☐	☑	☑
Nimesulide	☐	☑	☐

NSAID	Causes death after experimental treatment at the MLE	Associated with visceral gout in dead vultures	Associated with death after therapeutic treatment
Diclofenac/Aceclofenac	☑	☑	☐
Meloxicam	☒	☒	☒
Ketoprofen	☑	☑	☐
Flunixin	☐	☑	☑
Nimesulide	☐ planned	☑	☐
Carprofen	☑	☐	☑
Phenylbutazone	☐	☐	☑
Paracetamol	☐ planned	☐	☐
Analgin	☐ planned	☐	☐
Ibuprofen	☐ planned	☐	☐
Piroxicam	☐ planned	☐	☐
Tolfenamic acid	☐ planned	☐	☐
Mefenamic acid	☐	☐	☐

Meloxicam
Review of effects

- Can meloxicam replace all other NSAIDs?
- Is meloxicam safe to use in domesticated ungulates?
- Is meloxicam as effective as or more effective than other NSAIDs?

- Literature review of *in vivo* experimental studies and clinical trials reporting an effect of
  - Aceclofenac (n = 1)
  - Flunixin (n= 90)
  - Ketoprofen (n = 65)
  - Meloxicam (n = 117)
  - Nimesulide (n = 1)

- Variety of domesticated animals; and husbandry and veterinary situations
- Effects: positive, negative, mixed, none, non-conclusive

Meloxicam
Review of effects

	Positive	Negative	Mixed	No
Meloxicam	79%	3%	9%	7%
Aceclofenac	1 study	-	-	-
Flunixin	44%	9%	15%	28%
Ketoprofen	63%	5%	22%	8%
Nimesulide	-	1 study	-	-

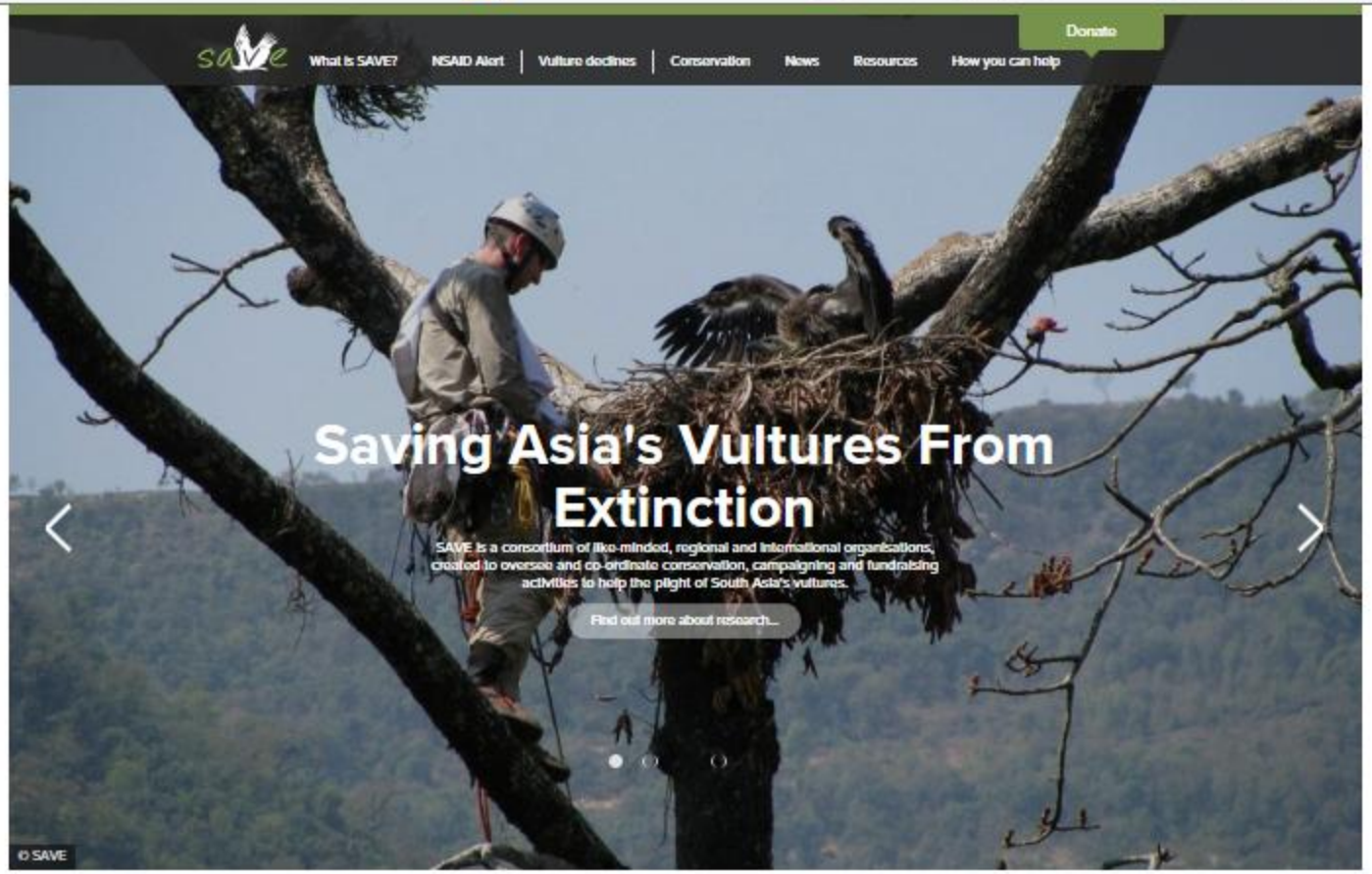
- More studies report a positive effect of meloxicam than of flunixin and ketoprofen
- Less studies report a negative, mixed or no effect of meloxicam than of flunixin and ketoprofen
- Only one study each examined aceclofenac and nimesulide

Meloxicam: Review of effects

- Meloxicam showed positive effects in
  - cattle, buffalo, horses, goats, sheep and dogs
  - clinical trials; and for infections, injuries, surgeries, breeding, husbandry (e.g. transporting and castrating)
- Meloxicam treatment
  - decreased pain, inflammation, stress and dysfunction
  - increased recovery rate, pregnancy rate, productivity and survival
  - Low levels of complications
- Veterinary meloxicam is manufactured in Bangladesh, India, Nepal and Pakistan
- *Meloxicam is a safe and effective veterinary drug; in fact it is safer and more broadly effective than aceclofenac, flunixin, ketoprofen and nimesulide*

NSAID Alert
Summaries and website

- We have released NSAID Alert summaries for aceclofenac, flunixin, ketoprofen and nimesulide
- These provide the evidence that each drug is toxic to *Gyps* vultures and that meloxicam is a safe and effective alternative
- These summaries and published papers referenced within are accessible from the NSAID Alert page on the SAVE website www.save-vultures.org
- We will continue to produce summaries on vulture-toxic and vulture-safe NSAIDs as the evidence is shown



NSAID ALERT!

save

SAVING ASIA'S VULTURES FROM EXTINCTION

NSAID Alert

Diclofenac is not the only vulture-toxic NSAID. Summaries of the evidence for the toxicity of other NSAIDs to vultures can be downloaded on our NSAID Alert page.

NSAID Alert

References

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Lunch

Enjoy!

Resume in...

NSAID Alert Discussion

Panel:	Mr. Arunachalam, DC India
	Mrs. N. Sultana, DGDA Bangladesh
	Mr. K. C. Santosh, DDA Nepal
	Dr. D. Swarup, formerly CRIG & IVRI
	Dr. V. Prakash, BNHS
Chairman:	Dr. Homi Khusrokhan, BNHS
Leader:	Prof. Rhys Green, RSPB CfCS

Topic 1

The procedures required for authorities to ban NSAIDs shown to be toxic to vultures.

Topic 2

The procedures required to temporarily suspend the use of NSAIDs not safety tested on vultures.

Topic 3

The procedures required to establish mandatory safety testing on vultures for all NSAIDs before approval for veterinary use.

Summary: Discussion in Pakistan

Dr. Aslam, DRA, Pakistan

Summary: Discussion in India

Mr. C. Arunachalam, DDC India

Vote of Thanks

Mr. Chris Bowden,

Programme Manager,

SAVE

Vote of Thanks

Dr. Deepak Apte,

Director,

BNHS, India

SAVING ASIA'S VULTURES
FROM EXTINCTION