One Health approach to use of veterinary pharmaceuticals

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Weak environmental assessments undermine regulations.

An estimated 6051 tons of active substances went into the production of veterinary pharmaceuticals (VPs) for the treatment of food animals in the European Union (EU) in 2004, including 5393 tons of antibiotics and 194 tons of antiparasitics (*1*). With global meat production projected to increase (*2*) and the growing market for companion animal pharmaceuticals (*3*), the use of VPs will continue to increase. Although VPs may benefit the health and welfare of domestic animals and the efficiency of food animal production, they can contaminate the environment through manufacturing, treatment of animals, and disposal of carcasses, offal, urine, feces, and unused products (*4*) (see the chart). This contamination is a threat to nontarget species, including humans. With Spain having recently authorized marketing of a VP that was banned in South Asia in the past decade in light of environmental impacts, we recommend strengthening of current procedures and addition of a more proactive, holistic, One Health approach applicable to all VPs.

VULNERABLE VULTURES. In the 1980s, the three *Gyps* vulture species endemic to South Asia were the most abundant large raptors in the world, but their populations were reduced to near extinction in the 1990s (*5*). The nonsteroidal anti-inflammatory drug (NSAID) diclofenac was identified (in 2004) as the primary cause of rapid declines in Pakistan, India, and Nepal. Low-cost diclofenac-based products were being widely administered to livestock. Sufficient residues remained in carcasses of treated animals to cause acute renal failure and death of vultures feeding on them. Lethal contamination of just 0.3 to 0.7% of ungulate carcasses could account for observed decline of one vulture species at 50% per year (*6*).

The government of India enacted a ban on production, importation, and sale of veterinary diclofenac products in 2006. Similar measures were taken in Pakistan, Nepal, and Bangladesh. This was facilitated by the identification of meloxicam as a suitable alternative drug that was safe for *Gyps* vultures. Over the past 8 years, vulture population declines in South Asia have slowed, and may have reversed in some areas (supplementary materials) (*7*, *8*).

Despite this history, the government of Spain authorized marketing of diclofenac as a VP for use in cattle, pigs, and horses in 2013. This authorization was in compliance with current EU guidelines. Spain is important for global conservation of avian scavengers, as it holds >95% of the European population of vultures, the entire population of the globally threatened Spanish Imperial Eagle (*Aquila adalberti*), and important numbers of Red Kites (*Milvus milvus*) (table S1 and fig. S1).

Spanish law allows carcasses of farm animals to be left in the field in some protected areas or to be taken to "muladares" (vulture feeding stations) to provide food for wildlife. By law, diclofenac should only be administered under veterinary supervision and should not be given to animals that are likely to enter the natural food chain. But Spain's livestock industry has around 25 million pigs and 5.7 million cattle, and diclofenac is licensed for use against many clinical conditions that occur in these animals. There has been a dramatic increase in veterinary use of NSAIDs in recent decades (*9*). Vulture populations are very sensitive to even very low levels of contamination. Thus, despite existing regulations, given the scale of use and the reality of imperfect compliance with regulations, it seems reasonable that diclofenac could still find its way into the vulture food chain, with potentially harmful outcomes.

Vultures have traditionally provided important ecosystem services, helping control disease and pests, recycling nutrients, and providing cultural inspiration and recreational value. It has been estimated that Spanish vultures remove >8000 tons of livestock carcasses per year alone, preventing release of greenhouse gases and providing economic savings estimated at €1.5 million ($1.86 million) (*10*).

European countries have important populations of other endangered avian scavengers, and these depend heavily on livestock carcasses in some areas (*11*). Consequences of use of NSAIDs are likely to occur beyond the borders of individual countries, as many species show pronounced seasonal and erratic movements (*12*) (fig. S2). The toxicity of diclofenac to most accipitriforms is largely unknown, but an eagle species, *Aquila nipalensis*, may be susceptible (*13*). The risk to avian scavengers has not been evaluated adequately, thus diclofenac should be suspended for veterinary use in the EU.

In response to concerns raised by members of the public, politicians, and conservation organizations, the European Commission will consider scientific advice on possible ef-

fects of veterinary medicines containing diclofenac on avian scavengers. This may lead to withdrawal of diclofenac for veterinary use in the EU and, it is hoped, convince other countries to follow.

A FLAWED APPROACH. Environmental risk assessment for new VPs is necessary for national licensing in EU countries. But there are approximately 2000 VPs in use in the EU, most of which have never been fully tested (*14*). VPs are exempt from assessment if they are used in a nonfood species, in a minor food species (i.e., all species except cattle, pigs, chickens, sheep for meat, and Atlantic salmon) if reared the same way as a major species for which an assessment already exists, or belong to certain product types (considered to be used for "a small number of animals in a herd or flock"): anesthetics; sedatives; injectable antibiotics (except those used for pigs, respiratory disease in cattle, or foot rot in sheep); injectable corticosteroids; hormones (except those that have a zootechnical use); and injectable NSAIDs (*15*). Assessment does not account for several key issues, many of which we remain largely ignorant of, including: effects on species other than the few tested, low-dose effects, chronic effects, interactive effects after exposure to multiple pharmaceuticals, exposure during vulnerable stages (such as gestation and development), rate of degradation of pharmaceuticals, and toxicity of metabolites (*4*).

Diclofenac would be exempt from environmental impact assessment because it is an injectable NSAID, despite its known toxicity in nontarget species such as vultures. Other NSAIDs used in the EU may also pose a risk to avian scavengers. Ketoprofen is nephrotoxic in African *Gyps* vultures at doses likely to be encountered when feeding on carcasses of ungulates given a standard veterinary dose (*16*), and carprofen and flunixin may also be nephrotoxic to *Gyps* vultures (*5*, *17*). NSAIDs are one of several categories of VPs that may pose a risk to nontarget species through environmental contamination. Others include parasiticides and their nontarget impact on vertebrates and invertebrates in dung, soil, and watercourses (*18*); and more broadly, the human health implications of antimicrobial resistance in environmental bacteria associated with large-scale antibiotic use in food animal production (*19*).

A ONE HEALTH MINDSET. We may never have the knowledge required to adequately assess environmental risk of VPs. Whereas we need to strengthen current systems of environmental impact assessment where possible, we also need to foster the precautionary principle and aim to prevent environmental contamination with VPs in the first place. We advocate "cradle-to-cradle" stewardship that promotes environmental responsibility; involves all sectors of society; and considers environmental effects during production, use, and disposal (see the chart).

General public. Increase public education regarding environmental effects of pharmaceuticals and personal care products (e.g., a brochure for South African farmers and land owners, explaining risks of VP-contaminated carcasses); promote take-back programs at pharmacies and veterinary clinics to facilitate appropriate disposal of unused medication [patients informed of environmental consequences of pharmaceuticals were more likely to return unused medicines for proper disposal (*20*)]; and use consumer purchasing power to encourage environmentally sustainable food animal production (e.g., eating-better.org).

Food retailers and restaurants. Source and promote food products of animal origin that are generated under environmentally sustainable conditions. Organizations like sustainweb.org give practical guidelines for restaurants and caterers to adopt a sustainable approach to food.

Professionals and scientists. Stimulate collaboration among veterinarians, pharmacologists, farmers, animal scientists, ecologists, and environmental scientists, who are often unaware of each other's work. These disciplines are integral for design, dispensing, and application of VPs and for creating animal husbandry systems that promote biosecurity and principles of hygiene and that contribute to the health of food animals and their consumers, while maintaining the integrity of the environment and safety for nontarget species. The Swedish Environmental Classification and Information System for Pharmaceuticals brings together the pharmaceutical industry, Swedish Medicine Products Agency, regional authorities, and physicians to provide tools for prescribing drugs in an environmentally conscious way (*21*). *Pharmaceutical industry*. Practice "green pharmacy" (*22*) by considering the environment at all stages of the pipeline: drug design, delivery, packaging, advertising, and marketing. The pharmaceutical industry already has moved toward products and processes that are more environmentally sustainable, e.g., by use of enzymes for some transformation reactions and use of continuous processes for primary and secondary pharmaceutical production (*23*).

Such stewardship for VPs would mirror similar programs proposed for human pharmaceuticals and personal care products (*22*, *24*) and would help restrict effects of pharmaceuticals to where they belong: in the target species. This integrated effort to link the health of people, animals, and the environment is a good example of the One Health approach, an important step toward a more sustainable society.

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Griffon Vultures at a feeding station in Lleida, Spain.
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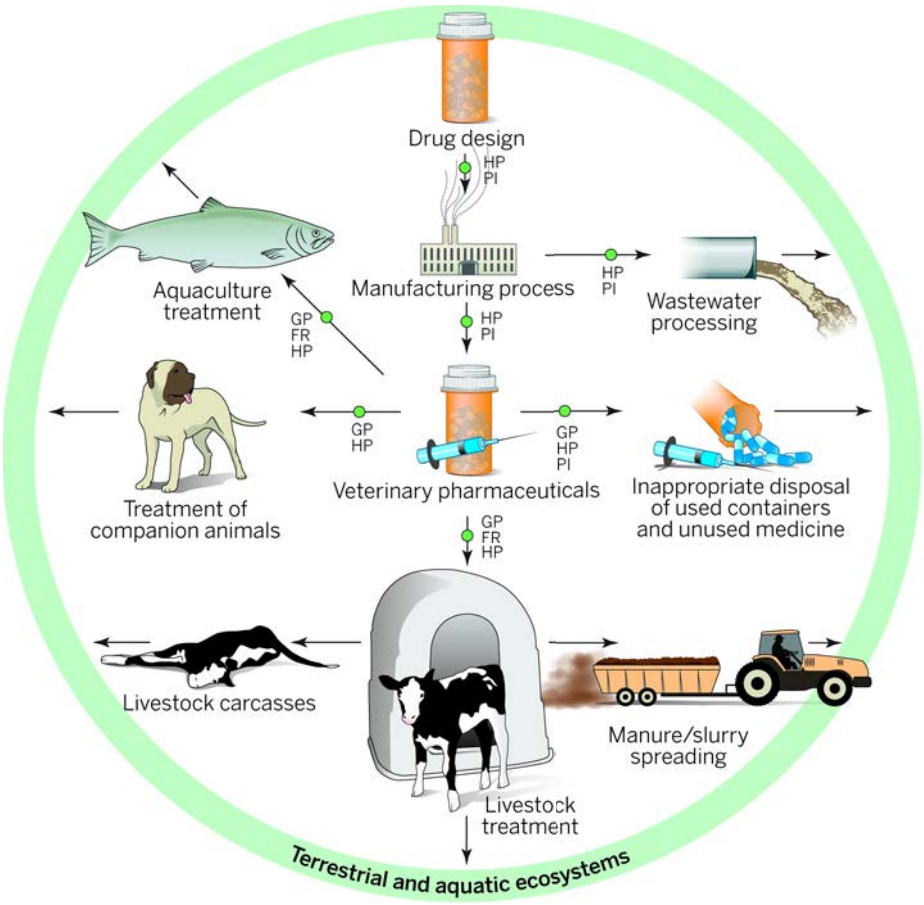

Major pathways of release of veterinary pharmaceuticals into the environment. Green dots represent control points where environmental contamination can be prevented or minimized. GP, general public; FR, food retailers; HP, health professionals and scientists, including veterinarians, pharmacologists, farmers, animal scientists, ecologists, and environmental scientists; PI, pharmaceutical industry. Based in part on (*4*).
ILLUSTRATION: P. HUEY/*SCIENCE*

SUPPLEMENTARY TEXT

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Additional text

Diclofenac in vultures in South Asia

In the 1980s, the three *Gyps* vulture species endemic to South Asia were the most abundant large raptors in the world (*1*), but during the 1990s, their populations were reduced to near extinction (*2*). The nonsteroidal anti-inflammatory drug (NSAID) diclofenac was identified in 2004 as the primary cause of rapid declines in Pakistan, India, and Nepal (*3*, *4*). Low-cost veterinary diclofenac-based products were being widely administered to livestock, some of which subsequently died. Sufficient residues remained in the carcasses of treated animals to cause acute renal failure and rapid death of vultures feeding on them.

Experimental administration of diclofenac to Oriental White-backed (*Gyps bengalensis*), African White-backed (*G. africanus*), Cape Griffon (*G. coprotheres*) and Eurasian Griffon (*G. fulvus*) vultures was followed by death 28 to 56 hours after exposure (*3*, *5*, *6*). Clinical signs were associated with increased serum alanine aminotransferase activity and hyperuricemia. Diffuse visceral gout was a consistent post mortem autopsy finding, with histology revealing disruption of renal architecture by tophi, and necrosis of proximal convoluted renal tubules; combined with the clinical signs, this was indicative of renal failure (*3*, *5*).

Because death rates of vultures are low under normal conditions, additional mortalities caused by veterinary drugs can have a profound population impact. Models indicate that contamination of just 0.34 to 0.74% of ungulate carcasses with lethal levels of diclofenac is sufficient to cause vulture populations to decline at about 50% per year, as observed for one species (*G. bengalensis*) in India and Pakistan (*7*). Using the set of

population modeling equations given on page 795 of reference (*7*), it can be shown that a vulture population could decline by half in just 6 years if the proportion of ungulate carcasses contaminated with a lethal dose of diclofenac is between one in one thousand (if the mean interval between meals F is assumed to be 4 days) and one in two thousand (for $F = 2$ days).

The Government of India enacted a ban on the production, importation, and sale of veterinary diclofenac products in 2006. Similar measures were taken in Pakistan, Nepal, and Bangladesh. This action was facilitated by the identification of meloxicam as a suitable alternative drug that was safe for *Gyps* vultures (*8*). Over the past 8 years, vulture population declines in South Asia have slowed and may have reversed in some areas (*9*–*11*).

Beyond Asia, evidence regarding diclofenac toxicity to vultures resulted in discussion between various stakeholders and prompted the Medicines Control Council of South Africa to deny registration authorisation for its veterinary use. The Council also mandated that a warning of potential vulture toxicity would be placed on package inserts of all NSAIDs with unknown toxicity (Vinny Naidoo, personal communication).

Fig. S1. Vultures and other avian scavengers at feeding stations in Spain. (**A**) A Bearded and a Cinereous Vulture among Griffon Vultures. (**B**) Cinereous Vulture and Common Raven and Griffon Vultures in the background. (**C**) Black Kites. (**D**) Egyptian Vulture with Griffon Vultures in the background. Photo credits: Jordi Bas (A), Antonio Atienza (B, C, D).

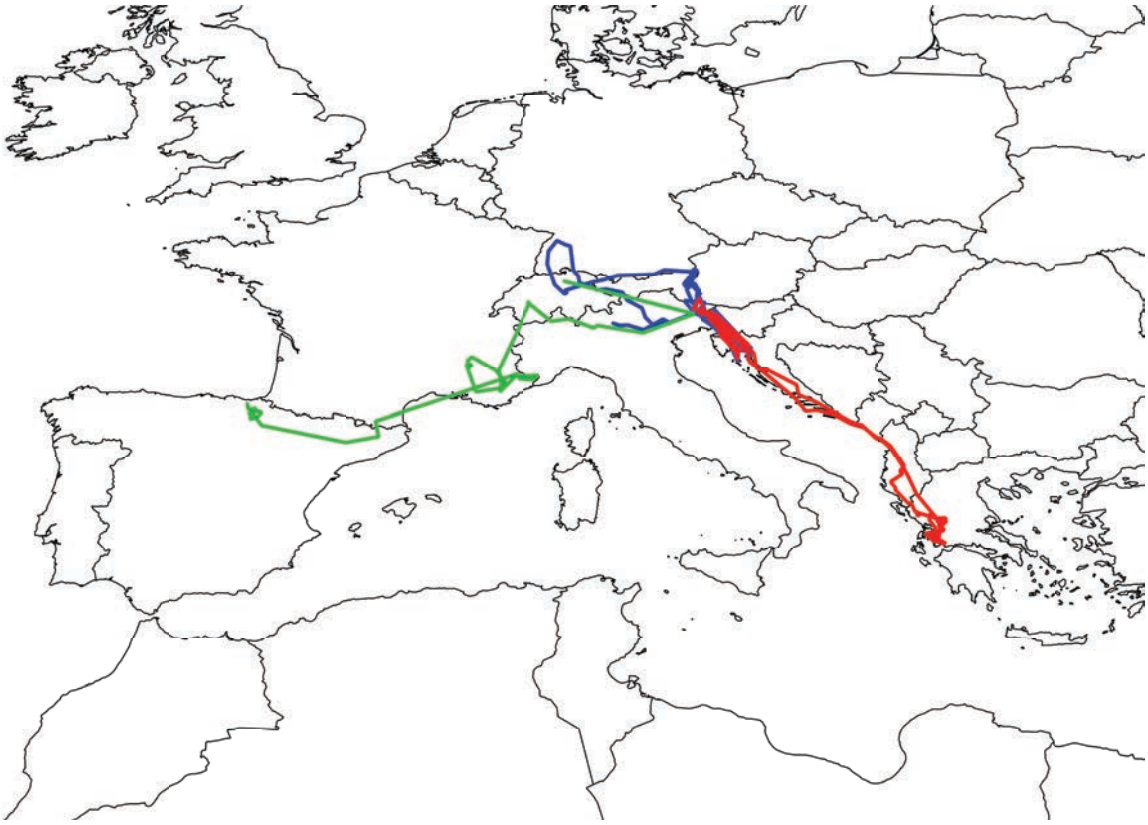

Fig. S2. Movements of three Griffon Vultures tracked with global positioning system (GPS) and global system mobile (GSM) telemetry, showing that each bird ranged between several countries in Europe. The transmitters (Vectronics, Germany) weighed about 190 g each, were solar powered, mounted on the back with a soft harness, and programmed to send a variable number (2 to 20) of daily locations (geographical coordinates and altitude), depending on the amount of solar energy available. Data were remotely transferred to operators (using GPS for mobile communications and the GSM network), and implemented with GPS Plus, a software package that allows the user to manage and configure transmitters and the ground-based terminal and to download, process, and store transmitter-collected data. The first bird (green line; transmission from 12 June 2011 to 1 January 2012, with 248 valid fixes) was an adult found exhausted in Tirol in June 2009, rehabilitated, and released. The second (red line; transmission from 20 September 2013 to 10 May 2014, with 1230 valid fixes) and third (blue line; transmission from 1 May 2014 to 20 July 2014, with 420 valid fixes) birds were immatures captured with a walk-in trap in northeast Italy in summer 2013. All birds were released in the vulture feeding point of the Riserva Natural Lago di Cornino (Udine, Italy; 46° 13′ 44″ N; 13° 01′ 20″ E). Birds were aged according to plumage characteristics or rings previously placed on chicks when they were still on the nest. Research was carried out with the collaboration and financial support of Riserva Naturale Lago di Cornino (Udine, Italy); National Park Hohe Tauern (Salzburg, Austria); Parco Natura Viva (Verona, Italy); Zoo Salzburg (Austria); University of Veterinary Medicine (Vienna, Austria); and Österreich Eulen und Greifvogel Station (Austria).

Table S1. European status of four obligate scavenger species. Sources (with modifications): (*12*, *13*)

Country	**Griffon Vulture**	**Cinereous Vulture**	**Bearded Vulture**	**Egyptian Vulture**
Albania	0	0	0	27*
Austria	0	0	3–4	0
Bulgaria	67	0	0	26
Croatia	141	0	0	0
Cyprus	2	0	0	0
France	1,443	28	46	80
Greece	270	28	6–7	12
Italy	95–100	0	8–9	6–7
FYRO Macedonia	16	0	0	21
Portugal	197–361	2–3	0	83
Serbia	130	0	0	0
Spain	24,609–25,541	2068	128	1,452–1,556
Switzerland	0	0	10	0
Ukraine	23–25	2–20	0	0
Total	26,993–28,096	2,128–2,147	201–204	1,707–1,812

*Numbers of breeding pairs.

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