

Research Article

An evaluation of the registration and use prospects for four candidate toxicants for controlling invasive mongooses (*Herpestes javanicus auropunctatus*)

Emily W. Ruell^{1,*}, Chris N. Niebuhr^{2,3}, Robert T. Sugihara² and Shane R. Siers²

¹USDA, APHIS, WS, National Wildlife Research Center, 4101 LaPorte Avenue, Fort Collins, CO 80521, USA

²USDA, APHIS, WS, National Wildlife Research Center, Hawaii Field Station, P.O. Box 10880, Hilo, HI 96721, USA

³Present address: Landcare Research, PO Box 69040, Lincoln 7640, New Zealand

Author e-mails: emily.w.ruell@usda.gov (EWR), niebuhr@landcareresearch.co.nz (CNN), robert.t.sugihara@usda.gov (RTS), shane.r.siers@usda.gov (SRS)

*Corresponding author

Citation: Ruell EW, Niebuhr CN, Sugihara RT, Siers SR (2019) An evaluation of the registration and use prospects for four candidate toxicants for controlling invasive mongooses (*Herpestes javanicus auropunctatus*). *Management of Biological Invasions* 10(3): 573–596, <https://doi.org/10.3391/mbi.2019.10.3.11>

Received: 2 November 2018

Accepted: 9 May 2019

Published: 20 July 2019

Handling editor: Frank H. Koch

Thematic editor: Catherine Jarnevic

Copyright: © Ruell et al.

This is an open access article distributed under terms of the Creative Commons Attribution License (Attribution 4.0 International - CC BY 4.0).

OPEN ACCESS

Abstract

The eradication or control of invasive small Indian mongooses from islands likely requires toxic baiting when removal by trapping proves insufficient. The one toxic bait currently registered for mongooses in the United States has relatively low palatability and efficacy for mongooses. Developing and registering a new pesticide can be very expensive, while funding for developing toxicants for mongooses is limited. Once registered, use of a toxic bait may be hindered by other factors, such as public opposition to an inhumane toxicant, poorer efficacy than expected, or if the toxic bait is difficult for applicators to apply or store. Therefore, we conducted a product feasibility assessment comparing the registration and use potential of toxic baits for mongooses containing either bromethalin, diphacinone, para-aminopropiophenone (PAPP), or sodium nitrite (SN). We estimated that a diphacinone bait would be the cheapest and fastest to register, and more application methods may be allowed compared to the others. On the negative side, we ranked diphacinone as the least humane toxicant of the four, largely due to a prolonged time to death following exposure and onset of symptoms. However, this interval also increases the probability that the antidote can be administered following an accidental exposure. If an alternative toxicant is required, use of a bromethalin, PAPP, or SN bait would likely be limited to bait stations or burrow baiting due to primary risks to non-target species. A bromethalin bait would be the cheapest and fastest to register of the three, particularly if a bait that is already commercially available proved efficacious for mongoose. However, we ranked bromethalin lower than PAPP or SN for overall humaneness. A PAPP bait would be slow and the most expensive to register. An SN bait would be challenging to formulate into a palatable bait with a reasonable shelf life. Although we focused on the U.S., mongooses are invasive in many parts of the world and the regulatory and use requirements for pesticides in other countries are generally comparable. In addition, our feasibility assessment can serve as a template or starting point for managers considering development of toxicant products for vertebrate pests.

Key words: humaneness, injurious wildlife, invasive species, mongoose, pest, pesticide, regulation, regulatory requirements, toxic baiting

Introduction

Many of the world's invasive vertebrate species were intentionally introduced by humans for biological pest control or for agricultural or commercial

reasons, but instead they caused native species extinctions, damaged ecosystems and crops, and spread diseases, resulting in large ecological and economic costs (Pimentel et al. 2000). Depending on the characteristics of the invasive species and location, successful control and eradication efforts against invasive populations may require the use of multiple management tools, including toxicants (Simberloff 2003).

The small Indian mongoose (*Herpestes javanicus auropunctatus* Hodgson, 1836; hereafter, mongoose) was intentionally introduced to the islands of Hawaii, Puerto Rico, and the United States Virgin Islands in the late 1800s through the early 1900s for the purpose of controlling rats (*Rattus* sp. Fischer, 1803) to protect sugarcane crops (Baldwin et al. 1952; Keith et al. 1989; Hays and Conant 2007; USFWS 2011; Berentsen et al. 2018). However, introduced mongooses decimated and continue to cause the decline of numerous native bird, mammal, amphibian, and reptile species on these islands (reviewed in Hays and Conant 2007; Barun et al. 2011; Berentsen et al. 2018). In addition, mongooses pose human health risks as some of the introduced populations carry and transmit zoonotic diseases, including rabies and leptospirosis (Everard et al. 1976; Everard and Everard 1992; Wong et al. 2012; Zieger et al. 2014; Berentsen et al. 2015). Pimentel et al. (2000) estimated that mongooses caused approximately \$50 million in damages each year in Puerto Rico and Hawaii.

Because of their impacts on native fauna and potential for disease transmission, mongooses were one of the first species listed as injurious wildlife under the Lacey Act of 1900 (18 U.S.C. §§ 42–43; USFWS 2017), which made it illegal to import, export, acquire, or transport mongooses in the U.S. or in any territory or possession of the U.S. (18 U.S.C. § 42). Laws in U.S. states and territories generally also prohibit the acquisition, possession, distribution, or release of any species classified as invasive, harmful, or injurious, including Hawaii (Hawaii Administrative Rules 13-124-3) and the Commonwealth of Puerto Rico (The New Wildlife Act of Puerto Rico, Law No. 241). The mongoose also makes the list of the top 100 of the world's worst invasive alien species from the Global Invasive Species Database from the International Union for Conservation of Nature (IUCN 2018).

Numerous strategies to reduce or remove invasive mongoose populations on islands, including trapping and toxic baiting, have been used over the years, mainly to reduce mongoose predation in and around sensitive native areas (e.g. ground nesting upland and sea bird colonies) (Barun et al. 2011; Sugihara et al. 2018; Berentsen et al. 2018). Trapping has been effective short-term at reducing predation risks in certain circumstances. However, trapping is labor-intensive, often expensive, only removes individuals from a limited area, and can ultimately prove ineffective due to the immigration of mongooses from outside the trapping areas (Hays and Conant 2007; Barun et al. 2011; Berentsen et al. 2018). As a result, toxic baiting has been

advocated as a way of increasing the probability of successfully controlling or eradicating mongooses (Barun et al. 2011; Sugihara et al. 2018). However, few toxicants have been developed or registered specifically for mongooses in the U.S. or elsewhere (Barun et al. 2011).

Here, we review the development and registration of mongoose toxicants in the U.S. to date. We then present a registration and use feasibility assessment comparing four of the most promising toxicants from a previous laboratory efficacy trial. The primary constraint considered in this assessment was cost, given that there has been little commercial interest in developing a toxic bait for mongoose in the U.S., so funding would be limited to public sources. Other constraints considered in the assessment were delays to registration, humaneness, antidote availability, and convenience-of-use of the toxicant. The purpose of this feasibility assessment is to help future research efforts select one or more of these toxicants for further development into an alternative toxic bait for mongooses with higher efficacy than what is currently available.

Background

Registered toxicants for mongooses

In the U.S., toxic baits for mongooses must be registered at the federal level by the U.S. Environmental Protection Agency (USEPA) as a pesticide under Section 3 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA; Public Law No. 61-152, 7 U.S.C. § 136) and then also by individual states and territories under their governing pesticide laws before they can be distributed and used. Within the limitations set forth by FIFRA Section 24(c), states can also register pesticides for distribution and use only within their state for pest problems that are local in nature and for which an appropriate federal registration is not already available (40 C.F.R. § 162). Registrations under Section 24(c) are also called Special Local Needs (SLN) registrations. Most of the time, SLN pesticides are identical in composition or formulation to a “parent” federal registration, but the SLN pesticide label allows for additional uses in that particular state than what might be allowed on the parent label.

To date, the only pesticides registered specifically for mongooses in the U.S. were three SLN pesticides registered in Hawaii in the 1990s. The active ingredient in all of these SLN registrations was diphacinone (CAS No. 82-66-6), which is a “first generation” anticoagulant primarily used for rodenticide baits and that typically requires multiple successive feedings to be lethal (USEPA 2015). Under FIFRA, a pesticide active ingredient is “...an ingredient which will prevent, destroy, repel, or mitigate any pest” (40 C.F.R. § 136(a)(1)). Diphacinone is highly toxic to mongooses with a median lethal dose (LD₅₀) of 0.18 mg per kg body weight (Keith and Hirata 1988a; Keith et al. 1989).

Studies conducted in the 1980s showed that diphacinone mixed into fresh meat baits was highly effective for mongooses (Keith et al. 1988; Keith and Hirata 1988b). Thus, the first SLN registration in Hawaii in 1991 was for a product named “Diphacinone Concentrate” (SLN Reg. No. HI-910004, EPA Reg. No. 12455-9), which was mixed by applicators into raw ground beef for a final concentration of 0.00025% diphacinone. This concentration was 20 times lower than the 0.005% diphacinone concentrations in rodenticide baits commercially available today (USEPA 2015). Although these fresh baits were efficacious, they were labor intensive to use and degraded quickly in the field (Sugihara et al. 2018). The SLN registration was eventually discontinued due to limited use.

The second SLN registration was a hard, waxy, grain-based, fish-flavored, rodenticide bait block named “Eaton’s® All Weather Bait Blocks® Rodenticide with Fish Flavorizer™” (0.005% diphacinone), first registered in 1997 for mongooses and rodents in Hawaii (SLN Reg. No. HI-970007, EPA Reg. No. 56-44). This bait appeared to have high efficacy for mongooses in two small-scale field applications on Oahu, Hawaii in 1998 (Smith et al. 2000). This SLN registration was eventually discontinued for unknown reasons, but it may also have been due to issues with bait longevity in the field and concerns about viable exotic plant seeds within the bait matrix (R. Sugihara, *pers. comm.*). The manufacturer also cancelled the parent Section 3 registration in October 2004.

The third SLN registration for mongooses in Hawaii is also a hard, waxy, grain-based, fish-flavored bait block (0.005% diphacinone) named “Ramik® Mini Bars Kills Rats and Mice”, which was first registered in 1998 (SLN No. HI-980005, EPA Reg. No. 61282-26). This SLN registration was still registered in Hawaii for use on both mongooses and rodents through 2018, and is being considered for renewal. Its use is restricted to bait stations in conservation areas with prior approval from the U.S. Fish and Wildlife Service. Bait stations are enclosed application devices that allow target species to access the bait, but prevent or limit access to humans and non-target species. This SLN registration is further classified as a restricted use pesticide (RUP; 7 U.S.C. § 136(d)). RUPs must be purchased and applied by certified applicators (40 C.F.R. § 136(e)), who are typically certified by the state in which the pesticide will be applied. However, this registered bait block had fairly low efficacy (20% mortality; $n = 10$) over a 5-day feeding period in a laboratory no-choice efficacy trial using wild-caught mongooses from Hawaii, which was likely due to low palatability and consumption of the bait rather than low toxicity to mongooses (Sugihara et al. 2018). This product remains the only registered toxicant available for mongoose control in the U.S.

Candidate toxicants for future research and development efforts

Additional research is needed to develop a toxic bait that is more effective for controlling mongooses in the U.S., but that also has acceptable non-

target risks, and is not prohibitively costly or time consuming to develop and register. An ideal toxic bait would also have a humane mechanism of action, an antidote for accidental poisonings, and be convenient for applicators to store and use. However, not all of these goals may be obtainable for the active ingredients available for mammal pests at this time.

In no-choice efficacy trials for mongooses, Sugihara et al. (2018) evaluate the efficacy of nine active ingredients available in commercial rodenticide baits registered in Hawaii and/or had been previously tested for mongoose or used for other mammalian pests in Australia and New Zealand. They identified the four active ingredients, out of nine tested, with the most potential for use in toxic baits for mongooses. The active ingredients bromethalin, diphacinone, and para-aminopropiophenone (PAPP) appeared to be the most efficacious for mongooses. Although sodium nitrite (SN) showed relatively low efficacy, SN was also considered to be promising if used in a different bait formulation due to its possessing other favorable characteristics relative to many of the other active ingredients tested.

Bromethalin (CAS No. 63333-35-7) is an acute neurotoxin that requires only a single feeding to result in mortality. Bromethalin is a non-anticoagulant active ingredient used in a number of rodenticide baits registered for rodents in the U.S. (USEPA 2016a). Sugihara et al. (2018) tested a hard, waxy bait block (0.01% bromethalin) that is commercially available for use in bait stations to control rats and mice (Tomcat® Brands, Motomco). This bait had an efficacy of 95% mortality ($n = 20$). The Tomcat bait block appeared to be relatively palatable to mongooses (average daily consumption was $\sim 19\%$ of the bait offered; Sugihara et al. 2018) despite that bromethalin suppresses appetite once a lethal dose has been ingested (Jackson et al. 1982). To our knowledge, bromethalin has not been tested in mongooses in any other bait formulations.

Diphacinone is found in a number of rodenticide baits registered in the U.S. (USEPA 2015). Diphacinone is the most studied active ingredient to date for mongooses, in part because it appears to be particularly toxic to them and causes no taste aversion (Keith et al. 1989; Smith et al. 2000; Sugihara et al. 2018). Sugihara et al. (2018) found that diphacinone mixed with minced chicken (0.005% diphacinone) was highly palatable to mongooses with 100% daily consumption of the bait offered ($n = 20$). The overall mortality rate was 70% for mongooses after a single day of feeding ($n = 10$), and 100% for mongooses over a 3-day feeding period ($n = 10$). Two commercially-available 0.005% diphacinone rodenticide baits from the Ramik rodenticide product line were also tested in this study over a 5-day feeding period: 1) the mini bar bait block currently registered in Hawaii for mongooses (described above), and 2) a hard, waxy pellet bait, which is only registered in Hawaii for rodents. These two diphacinone baits had much lower efficacy than the diphacinone mixed with minced chicken, likely due

to the much lower average daily consumption rates. Both of these baits are fish-flavored, grain-based, mold- and moisture-resistant baits optimized for gnawing rodents (Neogen Corporation 2012).

Unlike the first two active ingredients, PAPP (CAS No. 70-69-9) is not contained within any registered pesticides in the U.S., but is found in toxic baits registered for red foxes (*Vulpes vulpes* Linnaeus, 1758) and dingoes or wild dogs (*Canis lupus dingo* Meyer, 1973) in Australia (APVMA 2015), and for stoats (*Mustela ermine* Linnaeus, 1758) and feral cats (*Felis catus* Linnaeus, 1758) in New Zealand (ERMA 2011a; Eason et al. 2014). PAPP was also effective in canid ejector devices for red foxes and wild dogs in Australia (Allen 2019). PAPP is an acute, single-feeding toxicant that causes fatal methemoglobinemia at sufficient doses. PAPP is highly reactive and must be microencapsulated prior to mixing within a bait matrix in order to prevent taste aversion and chemical decomposition. Sugihara et al. (2018) tested three different microencapsulated PAPP (mePAPP) products mixed with minced raw chicken and found 0.15% PAPP to have the best efficacy (100% mortality; n = 10 animals) after a single feeding, with mongooses consuming about 60% of the bait offered on average.

Finally, SN (CAS No. 7632-00-0) is also not an active ingredient in any registered pesticides in the U.S., but an SN bait for feral swine (*Sus scrofa* Linnaeus, 1758) is being tested under an Experimental Use Permit (EUP; EPA Reg. No. 56228-EUP-42) in Texas and Alabama by the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (USDA APHIS). USDA APHIS and collaborators have generated or contracted all of the registration data required for SN as part of the development of a toxic bait for feral swine. SN baits are currently registered for common brushtail possums (*Trichosurus vulpecula* Kerr, 1792) and feral swine in New Zealand (NZEPA 2013) and are being reviewed for registration for feral swine in Australia (Linton Staples, *pers. comm.*). SN is also being tested for possible use in ejector devices for wild dogs and red foxes in Australia (Benjamin Allen, *pers. comm.*). Similar to PAPP, SN is an acute, single-feeding toxicant via fatal methemoglobinemia, but requires that a lethal dose is consumed over a relatively short period of time (i.e. a single feeding event or multiple feedings close together) because it is rapidly metabolized by the target animal (Lapidge and Eason 2010). Also like PAPP, SN is microencapsulated when used in baits to prevent taste aversion and degradation prior to consumption. SN rapidly dissociates to sodium and nitrite ions in the presence of moisture or acids within a bait matrix or the target animal. Microencapsulation of the SN masks the overly salty flavor and other aversive tastes or smells that result from the decomposition of nitrite into nitric oxides, which can slow or inhibit consumption by the target animal.

In Sugihara et al. (2018), two SN bait prototypes contained microencapsulated SN (meSN) mixed with minced raw chicken at a 5% SN concentration. Both baits had relatively poor efficacy (10 and 30% mortality, $n = 10$ per bait), which was likely due to insufficient bait consumption and sublethal dosing. Desiccation of the minced raw chicken occurred within a few hours after it was mixed with meSN, which is consistent with changes that would occur if the microencapsulation on the SN had been compromised. The proprietary microencapsulation formula was likely water soluble (Linton Staples and Duncan McMorran, *pers. comm.*). Thus, the SN would have become detectable to mongooses by taste, which likely reduced and slowed consumption of the baits during the 1-day feeding trial, limiting their efficacy. In prior studies on feral swine and common brushtail possums, SN that was not microencapsulated before it was mixed into a bait matrix has caused similar taste aversion, which resulted in low bait consumption and low to zero efficacy (Cowled et al. 2008; Foster et al. 2014; Shapiro et al. 2016).

An alternate bait matrix that better preserves the microencapsulation on the SN (e.g. an oil-based or dry matrix) might prevent taste aversion and improve efficacy. For example, a pen efficacy study of a bait for feral swine containing meSN (10% SN) within a peanut paste bait matrix resulted in 93% mortality after one night of feeding (Snow et al. 2017). Alternately, the use of a water-resistant microencapsulation material may also result in better efficacy in wetter bait matrices. The efficacy of SN at different concentrations and using a compatible microencapsulation formula and bait matrix has not yet been thoroughly tested for mongooses.

U.S. pesticide registration requirements

The USEPA must be provided with specific data from standardized product chemistry, ecological effects, toxicology, and environmental fate studies before they will consider registering any pesticide product (40 C.F.R. § 158). The proposed use pattern for an end-use product (EP; e.g., a toxic bait) also determines which set of registration data will be required (40 C.F.R. § 158.100). The majority of the data required for a registration application are for the technical grade of the active ingredient (40 C.F.R. § 158). A smaller subset of product chemistry, toxicology, and efficacy data are also required for registration of each new EP (e.g. a commercial “off-the-shelf” toxic bait or mix-on concentrate product). Additional data is required for the active ingredient when an EP registration application proposes a use pattern (e.g. a new use site, application method, or target species) that is not yet registered for that active ingredient. The studies that produce these data must usually conform strictly to USEPA’s study guidelines (40 C.F.R. § 158.70) and be performed in accordance with USEPA’s FIFRA Good Laboratory Practice (GLP) standards (40 C.F.R. § 160). Most of these studies can be contracted

from private laboratories that specialize in conducting guideline studies for pesticide registration. Individual study costs can range from a few hundred dollars to over a million dollars. Alternatively, applicants can choose to submit a data waiver request in which they provide justification for why a particular data submission is not necessary, applicable to the active ingredient or EP, or to the proposed application methods or use pattern for the EP (40 C.F.R. § 158.45). When USEPA reviews a registration application, they will accept or reject any data submission or waiver request. They may also require additional data on a case-by-case basis (40 C.F.R. § 158.75). All of this makes predicting the total registration data costs for a mongoose toxicant difficult.

A mongoose EP would be classified as having a terrestrial outdoor (non-food) use pattern. Some of the data for this use pattern might be waived by USEPA if the likely risks of the proposed use pattern (e.g. bait station only) and/or toxicity of the active ingredient and/or EP are low. Conversely, additional data might be required by USEPA if the product or use pattern exhibits high risk characteristics for human health, non-target species, or the environment. For mongoose EPs containing a registered active ingredient (i.e. an active ingredient that is already contained in a Section 3 registered EP), many if not all of the data requirements would have already been satisfied or waived for the active ingredient, and could be cited with the permission of the data owners. This also holds true for data on an EP if the EP is already registered for other target species.

The proposed application methods and/or toxicity of the active ingredient and EP and risks to non-target species also determine whether or not the EP will be classified as an RUP (40 C.F.R. § 152.170). Even EPs allowed for general use can have limitations on the label as to who can purchase and how they are allowed to use them. Some proposed application methods may never be registered if USEPA determines the risks to outweigh the benefits, or they may be limited to a small group of users under specific circumstances.

The general categories of data required for an EUP application for a field efficacy trial and then a Section 3 registration application for any mongoose EP are summarized below and are detailed in 40 C.F.R. § 158.

Laboratory and field efficacy data

EPs used to control vertebrates that may directly or indirectly transmit diseases to humans must provide product performance (efficacy) data for the EP for the target species, typically from both laboratory and field efficacy studies.

Product chemistry data

The product chemistry data requirements are fairly standardized for any unregistered active ingredient or EP. The “Group A” data requirements

describe the EP's composition (identify the active and inert ingredients), the production process for the active ingredient, the formulation process for the EP, and the formation of any impurities during the production or formulation process. The Group A data submission must also demonstrate the consistency of the EP and provide an enforcement analytical method for testing the EP for the concentration of the active ingredient and any impurities of toxicological concern. The "Group B" data requirements include the determination and description of a wide range of physical and chemical properties of the active ingredient and the EP, such as color, pH, vapor pressure, storage stability, etc.

Toxicology data

The toxicology data requirements for an active ingredient used in an EP with a terrestrial outdoor and non-food use pattern include a number of acute toxicity, subchronic toxicity, chronic toxicity, genetic toxicity, neurotoxicity, immunotoxicity, and other special human health effects studies. A standard suite of six acute toxicity studies ("the six-pack") and a subchronic dermal toxicity study are also required for each non-food use EP. These data are used by USEPA to assess hazards to humans and domestic animals that could potentially be exposed to the active ingredient through use of the EP.

Ecological effects (non-target risks) data

Ecological effects data requirements for a terrestrial outdoor use pattern include studies looking at the acute and chronic toxicity of the active ingredient to a variety of non-target bird, mammal, fish, and terrestrial and aquatic invertebrate species, and sometimes plants. These data are then used to assess primary and secondary risks to non-target species, including endangered species.

Primary risks are the risks to target or non-target animals that consume the EP or to non-target animals or plants that come into direct contact with the EP. Some EPs can cause emesis in animals, resulting in partially digested toxic bait on the ground. Primary risks are determined by the toxicity of the active ingredient to non-targets and on the amounts and routes of direct exposure non-targets could have to the active ingredient in the EP.

Secondary risks are risks to predatory or scavenging animals that feed on target or non-target animals that fed on toxic bait. Many active ingredients result in toxic tissue residues, which can then be consumed by predators or scavengers. Additionally, some active ingredients have the potential for bioaccumulation up the food chain.

Environmental fate data

The environmental fate data requirements are usually required for just the active ingredient. These data requirements include studies on the hydrolysis,

photodegradation, and soil and aquatic metabolism of the active ingredient, and the leaching and adsorption or desorption properties of the active ingredient in soils. These data are used to assess the distribution and persistence of the active ingredient and any degradation products in the environment.

Feasibility assessment

Following from Sugihara et al. (2018), we conducted a product feasibility assessment on theoretical EPs for mongooses containing bromethalin, diphacinone, PAPP, or SN, assuming that a sufficiently attractive and thus, efficacious EP could be developed for each one. The feasibility assessment included the predicted cost and time to register with USEPA and potential factors affecting operational use, such as relative humaneness, availability of an antidote, and overall convenience of use.

Cost and time feasibility

In order to compare the likely cost of registering an EP for mongooses containing one of these four active ingredients, we compiled the set of supporting data that would likely be required by USEPA for each EP under two registration scenarios that differed by which bait application methods would be allowed on the pesticide label. We focused on the data that would be required for a federal (Section 3) registration rather than a state-limited SLN, because mongooses are invasive to U.S. territories in addition to Hawaii. Furthermore, SLN registrations are only allowed for active ingredients (and inert or other ingredients) already found in a federally-registered pesticide (40 C.F.R. § 162.152), and two of the active ingredients reviewed here were not.

We determined the sets of studies still needed for each active ingredient for a range of scenarios by 1) using the registration data requirements outlined in 40 C.F.R. § 158, 2) reviewing what data are already available for each active ingredient and the data gaps identified by USEPA for bromethalin and diphacinone in recent registration reviews (USEPA 2015, 2016a), and 3) comparing to the data sets USEPA has required for rodenticides and other vertebrate pesticides with similar application methods (USEPA 2008, 2016b, 2018). For one set of scenarios, the label for the EPs would only allow two of the most conservative application methods for vertebrate pesticides, which are bait station and burrow baiting applications. USEPA generally considers these application methods to be the lowest risk for applicators, non-target species, and the environment (discussed in more detail below), and typically require smaller sets of supporting data (e.g. see USEPA 2016b). In the other set of scenarios, the data sets included the additional data that would likely be required if the labels allowed aboveground spot baiting and hand broadcast (thrown bait) applications in

addition to bait stations and burrow baiting. Aboveground applications outside of bait stations are typically considered higher risk (discussed below) and usually require more registration data to support these uses.

For any data on the active ingredient that was already accepted by EPA in support of existing diphacinone or bromethalin EPs, we assumed that the study cost would be zero, because the original data submitter would agree to share the data at no cost or the data would be old enough (> 15 years) that the original data rights had expired (40 C.F.R. § 152.93(b)(3)). For any remaining data requirements that were never submitted to USEPA, but would likely be required for the bait application method scenario, we estimated the study costs based on quotes obtained from private U.S. contract laboratories for 2018. Note that these study costs will gradually increase over time due to inflation and other market factors.

Because EPA could agree to waive some of the required data for a particular EP or active ingredient, we also provided a range of data costs for a least expensive (“best case”) and a most expensive (“worst case”) registration scenario (discussed in more detail below). Note that for any of the active ingredients, USEPA may require additional non-guideline ecological effects studies for an unregistered EP that is not similar to commercially-available rodenticide formulations (e.g. a new meat-based bait EP) to determine whether or not non-target wildlife or terrestrial invertebrates are at acute or chronic risk from the novel bait formulation, carcasses, or vomitus (if applicable). Because these studies are often only conditionally required or are non-guideline (i.e. not standardized), and customized for the specific active ingredient, it was not possible to estimate these potential additional study costs for this review.

USEPA has different statutorily-determined decision times (review periods) for EUP and Section 3 registration applications for registered and unregistered active ingredients and for amended or new uses under the Pesticide Registration Improvement Extension Act of 2018 (PRIA 4; P.L. 116-8). We determined the relevant decision times for each active ingredient and EP option using EPA’s online PRIA 4 Determination Decision Tree (USEPA 2019).

Bait station and burrow baiting applications

The use of enclosed bait stations for any aboveground applications can significantly reduce the risks to non-target animals, given that most cannot access the bait stations. “Tamper-resistant” enclosed bait stations are commonly required by USEPA for use of rodenticide EPs aboveground. However, large or strong animals may still be able to access these bait stations. Feral swine have been documented destroying plastic bait stations used in a conservation rodent control efforts in Hawaii, and consuming the diphacinone baits they contained (Pitt et al. 2005). However, for the sake of

this review, bait stations were presumed to be constructed of materials resistant to large animals when they are used in areas where these non-target species occur. Applications made only within the openings of burrows (burrow baiting) also reduce the risk to non-target species that cannot access the burrows. Because these application methods limit exposure of non-target animals, the registration data requirements for these application methods are typically fewer than for application methods that have greater risk of exposure.

Bromethalin and diphacinone already have EPs registered by USEPA for use in bait stations and below ground hand applications in burrows. The data requirements for these rodenticides based on these registered use patterns was recently reevaluated by USEPA's Hazard and Science Policy Council (USEPA 2016b) and during recent registration reviews by USEPA for both chemicals (USEPA 2015, 2016a). For an already-registered bromethalin or diphacinone EP under the best case scenario, new registration data would likely be limited to laboratory and field efficacy data on the EP for mongooses. Under the worst case scenario, a few additional data requirements for the active ingredient would be required in addition to the efficacy data on the EP based on what has not yet been submitted to or accepted by USEPA to date (USEPA 2015, 2016a).

For an unregistered bromethalin or diphacinone EP under the best case scenario, new registration data would include the laboratory and field efficacy data plus the standard product chemistry and acute toxicity data that are required for any new EP (assuming USEPA did not allow "bridging" or the use of data from similar EPs). Again, the worst case registration data cost estimates include the same few additional data requirements for the active ingredient based on what has not yet been submitted to or accepted by USEPA to date (USEPA 2015, 2016a).

However, it is not anticipated that any additional data on these active ingredients would be required for a mongoose EP with bait station or burrow baiting application methods. Therefore, the data costs are the lowest and USEPA review times are the shortest for EPs containing bromethalin or diphacinone when used in bait stations and burrow baiting applications only, and particularly for already registered EPs (Table 1).

Although SN is not a registered active ingredient (i.e., there are no registered EPs) with USEPA at this time, all of the registration data required by USEPA for SN for an EP used for bait station applications has already been submitted to USEPA or contracted by USDA APHIS as part of development of an SN EP for feral swine. Furthermore, given that nitrite is a component of the nitrogen cycle, and much is already known about the fate of nitrite in terrestrial and aquatic ecosystems, it is not anticipated that any additional environmental fate data would be required for an EP with a burrow baiting application method. Therefore, an unregistered SN EP for use in bait stations and burrow baiting applications would be similar in registration

Table 1. Total estimated registration data costs and EPA decision times (review periods) for end-use products (EPs; toxic baits) containing bromethalin, diphacinone, para-aminopropiophenone (PAPP), or sodium nitrite (SN) for use in bait station or burrow baiting applications only. Total registration data cost estimates include the data required for both the experimental use permit (EUP) and subsequent Section 3 registration applications. Best case scenarios assume USEPA will waive some data requirements as discussed under “Bait station and burrow baiting applications.” Worst case scenarios assume USEPA will not waive these data requirements.

Active ingredient	Registered or Unregistered EP	Total registration data cost scenarios ^a		Decision time ^b (months)	
		Best case	Worst case	EUP	Section 3
Bromethalin	Registered	\$125,000	\$200,000	6	4–10
	Unregistered	\$220,000	\$300,000	6	10–12
Diphacinone	Registered	\$125,000	\$200,000	6	4–10
	Unregistered	\$220,000	\$300,000	6	10–12
PAPP	Unregistered	\$810,000	\$5,800,000	16	21
SN	Unregistered	\$220,000	\$300,000	16	21

^aRegistration data cost estimates were summed from study quotes obtained from contract laboratories in 2018, and do not include initial research and development or pilot study costs on the EP.

^bUSEPA’s statutorily-determined decision times for different types of registration applications are specified under the Pesticide Registration Improvement Extension Act of 2018. Review periods begin once all the necessary data have been collected and the registration application is submitted to USEPA.

data costs to an unregistered bromethalin or diphacinone EP, but would have longer review times (Table 1) because USEPA has not yet reviewed and accepted data on the active ingredient.

In contrast to the other three active ingredients, a great deal of registration data is still missing for the unregistered active ingredient PAPP. Relatively little registration data that meets USEPA’s study guidelines or that was conducted under FIFRA GLPs or equivalent was available for PAPP from the registrations of PAPP products in Australia (APVMA 2015) or New Zealand (ERMA 2011b). The best case estimate of registration costs for PAPP assumed that USEPA would accept all of the data waiver requests that could conceivably be justified or studies in the published literature that are close but do not fully meet the USEPA’s guideline requirements. The worst case estimate for PAPP assumed that only the most suitable data available from the Australian or New Zealand registrations would be accepted by USEPA, and almost all of the other data requirements would require new GLP studies. Even under the best case scenario, the cost to register a PAPP EP used for bait stations or burrow baiting applications would likely be many times more expensive than the cost to register a bromethalin, diphacinone, or SN EP (Table 1). USEPA review times are also many months longer for a PAPP EP than for a bromethalin or diphacinone EP, but the same as for an SN EP (Table 1).

Aboveground spot baiting and hand broadcast applications

Primary risks to non-target animals are a major concern for a vertebrate EP applied aboveground and outside of a bait station, particularly for acute, single-feeding toxins when non-target animals could easily consume a lethal dose within the bait exposure period (USEPA 1998, 2008, 2016a). An EP that allowed aboveground spot baiting or hand broadcast applications would likely require additional ecological effects and environmental fate data

Table 2. Total estimated registration data costs and EPA decision times (review periods) for end-use products (EPs; toxic baits) containing bromethalin, diphacinone, para-aminopropiophenone (PAPP), or sodium nitrite (SN) for use aboveground spot baiting or hand-broadcast applications in addition to bait station and burrow baiting applications. Total registration data cost estimates include the data required for both the experimental use permit (EUP) and subsequent Section 3 registration applications. Total estimated data costs include those listed Table 1. Best case scenarios assume USEPA will waive some data requirements as discussed under “Aboveground spot baiting and hand broadcast applications”. Worst case scenarios assume USEPA will not waive these data requirements.

Active ingredient	Registered or Unregistered EP	Total registration data cost scenarios ^a		Decision time ^b (months)	
		Best case	Worst case	EUP	Section 3
Bromethalin	Registered	\$172,000	\$430,000	6	15
	Unregistered	\$267,000	\$530,000	6	15
Diphacinone	Registered	\$125,000	\$200,000	6	9–15
	Unregistered	\$220,000	\$300,000	6	10–15
PAPP	Unregistered	\$1,040,000	\$6,750,000	16	21
SN	Unregistered	\$275,000	\$740,000	16	21

^aRegistration data cost estimates were summed from study quotes obtained from contract laboratories in 2018, and do not include initial research and development or pilot study costs on the EP.

^bUSEPA’s statutorily-determined decision times for different types of registration applications are specified under the Pesticide Registration Improvement Extension Act of 2018. Review periods begin once all the necessary data have been collected and the registration application is submitted to USEPA.

compared to bait station or burrow baiting uses. These data are typically required for the active ingredient rather than for the EP, and are used by USEPA in standardized risk models.

Bromethalin, SN, and PAPP are acute, single-feeding toxicants that do not currently have registered EPs that allow aboveground baiting outside of bait stations or are unregistered active ingredients with USEPA. Under the best case scenario for an EP containing the registered active ingredient bromethalin, additional registration data required by USEPA would likely include a subset of the unfilled ecological effects or environmental fate data on the active ingredient (for data gaps, see USEPA 2016a). Under the worst case scenario, data required would include almost all of the unfilled ecological effects or environmental fate data on the active ingredient. The difference between the best case and worst case scenarios for the unregistered active ingredient SN and PAPP is how many data waiver requests would be accepted for the full set of ecological effects and environmental fate data requirements on the active ingredient.

Under these scenarios, EPs containing bromethalin, SN, or PAPP would likely be the most expensive of the four active ingredients to register for mongooses for aboveground spot baiting or broadcast application methods, with PAPP being the most expensive of the three (Table 2). Even with submission of all required data, USEPA would still likely limit broadcast applications of an EP containing an acute, single-feeding toxicant to areas where non-target animals could be excluded or were unlikely to be exposed to or at primary risk from the bait itself (e.g. see the USEPA (2008) risk assessment for rodenticides).

In contrast, the primary risks from aboveground spot or broadcast baiting are often reduced for active ingredients that require multiple feedings to achieve toxicity and that have relatively short persistence of

residues in tissues (USEPA 1998, 2015). Diphacinone is the only active ingredient of the four reviewed here that requires multiple feedings to be toxic, lowering primary risks, and the secondary risks for diphacinone are lower than for other commonly used rodenticide anticoagulants (Fisher et al. 2003; McLeod and Saunders 2013; USEPA 2015). However, diphacinone likely poses higher secondary risks to non-target species, particularly scavengers, than the other three active ingredients evaluated here (Eason et al. 2014; USEPA 2016a; Shapiro et al. 2018).

USEPA currently allows aboveground spot baiting and hand broadcast uses for a number of commercially-available diphacinone rodenticide baits, and aerial broadcast uses in conservation areas (e.g. Diphacinone-50: Pelleted Rodenticide Bait for Conservation Purposes; USEPA Reg. No. 56228-35; USEPA 2015). Therefore, it is likely that all of the required registration data for diphacinone for these types of application methods has been submitted to or waived by USEPA, and no additional registration data would be required for an EP containing diphacinone, assuming the concentration of diphacinone was at or below the concentration in currently registered EPs (Table 2). Because of this, the EPA review times under PRIA 4 would also be the shortest for diphacinone.

Operational feasibility

Humaneness

Under FIFRA, the humaneness of a toxicant's mechanism of action is not considered during the EPA's review for registration of a pesticide in the U.S. However, if an EP is not perceived to be humane, the extent that it is used on the ground could be limited by lack of support from stakeholders and potential users, and by lack of public acceptance of control efforts, particularly when the target species is a mammal.

We compared the relative humaneness of the four active ingredients using several metrics commonly evaluated for toxicants, including level of awareness after onset of symptoms, clinical signs of distress or observable symptoms prior to death, severity of symptoms, duration of symptoms (time period when first symptoms appear until death), and time to death. These data were compiled from the literature for mongooses (Sugihara et al. 2018) and a representative group of other mammalian species (Table 3; Jackson et al. 1982; Savarie et al. 1983; Dreikorn and O'Doherty 1984; Dorman et al. 1990; Marks et al. 2004; Eason et al. 2010; IMVS 2010; Landcare Research 2010; Foster 2011; McLeod and Saunders 2013; USEPA 2015, 2016a; Shapiro et al. 2016; Snow et al. 2017; Allen 2019). In order to compare the four active ingredients, we gave each a rank order from 1 (most humane) to 4 (least humane) for each humaneness metric (Table 4). When it was unclear which of two active ingredients ranked higher or lower (e.g. it was difficult to determine whether the symptoms of the first

Table 3. Humaneness metrics evaluated for each active ingredient from data compiled from the literature for a range of carnivorous and omnivorous mammalian species.

	Active ingredient			
	Bromethalin	Diphacinone	Para-aminopropiophenone (PAPP)	Sodium nitrite (SN)
<u>Humaneness metric</u>				
Mode of action	Neurotoxin	Anticoagulation	Methemoglobinemia	Methemoglobinemia
Level of awareness after onset of symptoms	Not reported, assumed conscious until death	Conscious until death	Loss of responsiveness occurs with increase in symptoms Loss of consciousness occurs prior to death	Loss of responsiveness occurs with increase in symptoms Loss of consciousness occurs prior to death
Clinical signs of distress or observable symptoms prior to death	Salivation Hyperactivity Hyperesthesia Myoclonia Vocalization Lethargy Hind-leg weakness Tremors Lateral recumbence Convulsions Seizures Paralysis Semicoma	Internal hemorrhage External hemorrhage Anorexia Dyspnoea Hypersensitivity Tremors Emesis Abnormal movement Lateral recumbence	Lethargy/weakness Salivation Nausea Emesis Hyperventilation Dyspnoea Cyanosis Vocalization Lateral recumbence Paddling/writhing Seizures	Lethargy/weakness Salivation Nausea Emesis Breathlessness Dyspnoea Pale skin Cyanosis Tremors Incoordination Lateral recumbence Paddling/writhing Seizures
Severity of symptoms	Severe to extreme	Severe to extreme	Mild to extreme	Mild to extreme
Duration of symptoms (period from first symptoms to death)	< 1–3 days	1–2 days to weeks	Minutes to hours	Minutes to hours
Time to death	< 1–4 days	3–21 days	< 1 hour–< 1 day	< 1 hour–< 2 days
<u>Species represented^a</u>	Domestic cat Domestic dog House mouse Mongoose Norway rat	Ferret House mouse Mongoose Norway rat	Coyote Domestic cat Domestic dog Ferret Mongoose Red fox Stoat Wild dog	Common brushtail possum Feral swine Mongoose Raccoon

^aScientific names: common brushtail possum (*Trichosurus vulpecula* Kerr, 1792); coyote (*Canis latrans* Say, 1823); domestic cat (*Felis catus* Linnaeus, 1758); domestic dog (*Canis lupus familiaris* Linnaeus, 1758); feral swine (*Sus scrofa* Linnaeus, 1758); ferret (*Mustela putorius furo* Linnaeus, 1758); house mouse (*Mus musculus* Linnaeus, 1758); mongoose (*Herpestes javanicus auro-punctatus* Hodgson, 1836); Norway rat (*Rattus norvegicus* Berkenhout, 1769); raccoon (*Procyon lotor* Linnaeus, 1758); red fox (*Vulpes vulpes* Linnaeus, 1758); stoat (*Mustela ermine* Linnaeus, 1758); wild dog *Canis lupus dingo* Meyer, 1973).

active ingredient were more severe or caused more distress than the symptoms of the second active ingredient), both active ingredients were given the average of the two ranks they would have held. Overall humaneness was then compared across active ingredients based on the summed rank score for the five metrics.

Diphacinone ranked the least humane overall, primarily due to the longer duration of symptoms and time to death compared to bromethalin, which was ranked second to last. SN and PAPP were tied for most humane because their mode of action (fatal methemoglobinemia) generally causes

Table 4. Relative rank (1–4) of the four active ingredients for each humaneness metric and their overall humaneness rank (the sum total).

Humaneness metric	Relative rank ^a			
	Bromethalin	Diphacinone	Para-aminopropiophenone (PAPP)	Sodium nitrite (SN)
Level of awareness after onset of symptoms	3.5	3.5	1.5	1.5
Clinical signs of distress or observable symptoms	3.5	3.5	1.5	1.5
Severity of symptoms	3.5	3.5	1.5	1.5
Duration of symptoms (period from first symptoms to death)	3	4	1.5	1.5
Time to death	3	4	1.5	1.5
Overall humaneness rank (sum total)	16.5	18.5	7.5	7.5

^aWhen two active ingredients tied in rank order or were difficult to rank (e.g. it was difficult to determine which symptoms were the most severe), we assigned the two active ingredients the average of the two ranks they would have held.

symptoms of lower severity and of shorter duration compared to the other two active ingredients, and because fatally dosed animals generally fall unconscious prior to the onset of the most severe symptoms.

Antidotes for accidental exposure

The four active ingredients also vary in the availability and efficacy of an antidote for humans or non-target animals in the event of an accidental poisoning, which might also affect public acceptance of a toxic bait, particularly one applied outside of bait stations or burrows. Bromethalin has no antidote in the event a toxic dose is ingested, but supportive therapies can limit or prevent toxicosis if administered quickly enough (Dorman et al. 1990; Coppock 2013; Rubinstein and Weinberg 2014). The antidote for diphacinone is vitamin K, which can be administered and still be effective for a longer period of time, largely because diphacinone is generally a slower acting toxicant that requires multiple feeding events (USEPA 2008, 2015; Baldwin et al. 2016). The antidote for a toxic dose of either PAPP or SN is methylene blue, which must be quickly administered intravenously due to the rapid onset and lethality of severe methemoglobinemia (NZEPA 2013; APVMA 2015; Shapiro et al. 2016).

Convenience of use

If an EP is not easy to use or store, toxic baiting efforts for mongooses are more likely to be inconsistently implemented or eventually abandoned. EPs that are classified as general use (unclassified) by USEPA are the easiest to purchase and use. EPs containing any of these four active ingredients could likely be classified as general use when only utilized within tamper-resistant bait stations and for burrow baiting by hand. However, these baiting application methods are more labor intensive than hand spot baiting and hand broadcast application methods.

Due to the primary risks of bromethalin, SN, and PAPP to most non-target vertebrate species, USEPA is unlikely to approve their widespread use aboveground and outside of bait stations (apart from rare circumstances

where non-target animals could be excluded or were not at risk from the EP itself). Diphacinone rodenticides are already registered for these application methods in conservation rodenticide baits and typically require multiple feedings for toxicity (USEPA 2015). Therefore, a diphacinone EP for mongooses could likely be registered for these application methods, given that the application rates would likely be lower than for rodents. However, like the diphacinone conservation rodenticide baits, any diphacinone EP for aboveground spot baiting or broadcast applications for mongooses would likely be classified as an RUP (at least for these application methods), due to the secondary risks to non-target animals (40 C.F.R. § 152.170(c); USEPA 2015). Furthermore, a diphacinone EP could still pose significant primary risks to non-target species if the bait palatability was universally high (e.g. Pitt et al. 2005). An RUP classification would make an EP less convenient to use compared to a general use EP, because applicators have to be certified by their state in the appropriate certification categories.

Furthermore, a mongoose EP must also be reasonably shelf-stable and resistant to degradation in hot or wet environments in order to be worth the effort from a manufacturing, distribution, marketing, or end-user standpoint. Although a fresh bait would likely be the most attractive to mongooses, it is highly perishable and logistically infeasible for larger scale applications, which is why the previous fresh diphacinone bait SLN registration was eventually abandoned (Pitt and Sugihara 2009; Barun et al. 2011; Sugihara et al. 2018). Longevity is particularly important for surveillance or rapid response scenarios where bait is likely to go unconsumed for long periods of time.

Thus, the ideal bait matrix from a palatability standpoint cannot outweigh other convenience-of-use factors and may not be necessary from an efficacy standpoint. A variety of bait flavors have been shown to be attractive to mongooses as they are opportunistic generalists (Pitt and Sugihara 2009; Berentsen et al. 2014, 2018; Pitt et al. 2015). Mold-resistant rodenticide EPs with a long shelf life have already been developed for bromethalin and diphacinone, and could potentially be modified to appeal more to mongooses while still retaining these characteristics. EPs with comparable stability have not yet been developed or registered in the U.S. for PAPP and SN. The fact that greater concentrations of PAPP and SN are required for toxicity for mongooses (Sugihara et al. 2018) and that they both require microencapsulation to mask their presence and slow their degradation also complicate EP development efforts for these two toxicants.

Recommendations and discussion

Our feasibility assessment did not indicate a consistent winner among the four active ingredients when looking across all of the criteria or constraints

we considered. Therefore, because registration data costs are a hard constraint and will likely rely on limited public funds, and the need for an alternative toxicant is time sensitive, we prioritized registration data costs and decision times over other factors when making recommendations on further product development efforts. However, we further discuss the relative advantages or disadvantages of the other active ingredients in the event that an alternative active ingredient is needed for unforeseen reasons or to diversify the options available in the future.

Our feasibility assessment indicated that an EP containing diphacinone would be among the least expensive to register and has several additional advantages over a bait containing one of the other three active ingredients. First, because it is already a registered active ingredient for all of the application methods considered here, EPA's decision times would be among the shortest. Furthermore, because diphacinone is the only active ingredient of the four that usually requires multiple feedings for lethality (at least for most species) and there is an effective antidote, a diphacinone EP likely poses the lowest primary risk to non-target species (Baldwin et al. 2016). Although normally this characteristic might also be considered disadvantageous when used in bait stations compared to acute toxicants in terms of efficacy in the target species, diphacinone is particularly toxic to mongooses compared to other mammals, and often does not require a second or third feeding for lethality (Sugihara et al. 2018).

Any completely novel bait matrix for mongooses for any of the active ingredients would likely require a great deal of research and development work on the formulation before any of the registration data required for the EP can be completed. These development times and costs were not estimated in this review, but can be substantial. Therefore, an additional advantage that a diphacinone EP potentially has over a PAPP or SN bait, but perhaps not over a bromethalin bait, is that multiple shelf- and field-stable diphacinone rodenticide EPs are already registered in the U.S. and manufactured commercially. One of these EPs could potentially be more palatable and have higher efficacy than the SLN diphacinone bait currently registered in Hawaii for mongooses. Given that mongooses are particularly sensitive to diphacinone, an EP with increased palatability and higher bait consumption rates may not require several days of feeding, and shortened exposure periods could further reduce non-target risks.

A diphacinone EP did have some disadvantages in our feasibility assessment compared to the others when applied in bait stations and in burrows. When used in bait stations and for burrow baiting, the other three active ingredients would likely pose much lower secondary risks to non-targets consuming tissue residues of animals that had consumed the bait compared to a diphacinone EP (ERMA 2011b; Shapiro et al. 2018; USEPA 2008, 2015, 2016a). In addition, diphacinone was ranked the least humane overall of the four active ingredients in our humaneness assessment,

which could hinder future use in the field due to public opposition. However, given that three diphacinone SLN products have been registered and used to control mongooses in Hawaii to date and mongooses remain a priority species for removal, there is no indication that public resistance will be an issue for a future diphacinone EP for mongooses.

If an alternative active ingredient is needed for use in bait stations or burrow baiting applications, our feasibility assessment indicated that a bromethalin EP would be more humane than a diphacinone EP and would be cheaper and faster to register than a PAPP or SN EP. Further investigation and testing of existing bromethalin EPs is advised if developers have very limited funds for registration and need the product available quickly. However, we ranked bromethalin as less humane than SN and PAPP, and bromethalin does not have an antidote.

A PAPP or SN EP for use in bait stations and burrow baiting applications had some advantages relative to a diphacinone or bromethalin EP, if sufficient resources were available for registration. Of the four active ingredients, we ranked PAPP as one of the most humane for mongooses. There are also PAPP EPs that are already developed for carnivores and commercially available in Australia that might prove efficacious for mongooses as well. However, we estimated that a PAPP EP would be many times more expensive and one of the slowest to register relative to the other active ingredients largely because PAPP is an unregistered active ingredient and a lot of the registration data that would be required in the U.S. are lacking. Development of a PAPP EP for mongoose control will likely only be feasible in the U.S. if the registration data are generated for another target species with a larger commercial market. In contrast, an SN EP would be relatively inexpensive to register, but one of the slowest as an unregistered active ingredient. We also ranked SN as one of the most humane toxicants for mongooses. However, substantial additional research (pilot studies) and development efforts may be required to make an SN EP sufficiently shelf-stable and palatable for mongooses.

For any use pattern aboveground and outside of bait stations, such as spot baiting or hand broadcast application methods, a diphacinone EP has far and away the best chance for registration, and would be the least expensive and fastest to register of the four. Low primary risk to non-target species is critical for registration of an EP aboveground and outside of bait stations in places where vulnerable non-target species are present, which includes most of the places where toxic baiting for mongooses would be needed. A number of diphacinone EPs for rodents are already registered for broadcast uses in a variety of non-crop use sites in the U.S., including conservation areas. However, it should be noted that these types of application methods would almost certainly result in an RUP classification and require certified applicators, regardless of which active ingredient the EP contained.

Future testing and development efforts in the U.S. can use this assessment to develop an alternative EP for mongooses using one of these four active ingredients, or to utilize a similar approach to identify and compare the registration and use constraints of alternative active ingredients, if needed. The intended use patterns, including an evaluation of the relative merits of the application method such as bait station versus broadcast delivery, could also influence the selection of an active ingredient. Although our discussion is specific to the registration process in the U.S., other countries where mongooses are invasive usually have similar constraints and requirements (e.g. Costa Rica, Croatia, Japan, and Netherland Antilles), making consideration of our assessment worthwhile in an international context. Finally, despite being specific to selection of a toxicant for mongooses, this review may serve as a useful primer and template for managers considering development of toxicant products for other vertebrate pest species.

Acronyms and abbreviations

CAS	Chemical Abstracts Service
C.F.R.	Code of Federal Regulations
EP	End-use product
EUP	Experimental Use Permit
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
GLP	Good Laboratory Practice
mePAPP	microencapsulated para-aminopropiophenone
meSN	microencapsulated sodium nitrite
PAPP	Para-aminopropiophenone
PRIA 4	Pesticide Registration Improvement Extension Act of 2018
RUP	Restricted use pesticide
SLN	Special Local Need
SN	Sodium nitrite
U.S.C.	United States Code
USDA APHIS	U.S. Department of Agriculture, Animal and Plant Health Inspection Service
USEPA	U.S. Environmental Protection Agency

Acknowledgements

We thank Dr. Benjamin Allen and two anonymous reviewers for their thoughtful suggestions for improvements to this paper. This work was funded by the Hawaii Department of Land and Natural Resources Division of Forestry and Wildlife and the USDA APHIS Wildlife Services, National Wildlife Research Center.

Conflicts of interest

The authors declare no conflicts of interest.

References

- Allen BL (2019) Para-aminopropiophenone (PAPP) in canid pest ejectors (CPEs) kills wild dogs and European red foxes quickly and humanely. *Environmental Science and Pollution Research*, <https://doi.org/10.1007/s11356-019-04818-7>
- APVMA (2015) Australian Pesticides and Veterinary Medicines Authority (APVMA). Public Release Summary on the Evaluation of the New Active 4-aminopropiophenone (also known as para-aminopropiophenone (PAPP)) in the Products Foxecute Fox Bait & PAPP Wild Dog Bait. APVMA Product Numbers 65095 and 65094. APVMA, Australia. https://apvma.gov.au/sites/default/files/publication/18771-papp_public_release_summary.pdf (accessed 22 August 2018)
- Baldwin PH, Schwartz CW, Schwartz ER (1952) Life history and economic status of the mongoose in Hawaii. *Journal of Mammalogy* 33: 335–356, <https://doi.org/10.2307/1375771>
- Baldwin RA, Meinerz R, Witmer GW (2016) Cholecalciferol plus diphacinone baits for vole control: a novel approach to a historic problem. *Journal of Pest Science* 89: 129–135, <https://doi.org/10.1007/s10340-015-0653-3>
- Barun A, Hanson CC, Campbell KJ, Simberloff D (2011) A review of small Indian mongoose management and eradications on islands. In: Veitch CR, Clout MN, Towns DR (eds), *Island Invasives: Eradication and Management*, Proceedings of the International Conference on Island Invasives. IUCN, Gland, Switzerland, pp 17–25
- Berentsen AR, Johnson SR, VerCauteren KC (2014) Bait matrix flavor preference by mongoose (*Herpestes auropunctatus*) in Puerto Rico: Implication for oral rabies vaccination. *Caribbean Journal of Science* 48: 52–58, <https://doi.org/10.18475/cjos.v48i1.a8>
- Berentsen AR, Johnson SR, Gilbert AT, VerCauteren KC (2015) Exposure to rabies in small Indian mongooses (*Herpestes auropunctatus*) from two regions in Puerto Rico. *Journal of Wildlife Diseases* 51: 896–900, <https://doi.org/10.7589/2015-01-016>
- Berentsen AR, Pitt WC, Sugihara RT (2018) Ecology of the small Indian mongoose (*Herpestes auropunctatus*) in North America. In: Pitt WC, Beasley JC, Witmer GW (eds), *Ecology and Management of Terrestrial Vertebrate Invasive Species in the United States*. CRC Press, Boca Raton, Florida, USA, pp 251–267, <https://doi.org/10.1201/9781315157078-12>
- Coppock R (2013) Advisory: bromethalin rodenticide - no known antidote. *The Canadian Veterinary Journal* 54: 557–558
- Cowled BD, Elsworth P, Lapidge SJ (2008) Additional toxins for feral pig (*Sus scrofa*) control: identifying and testing Achilles' heels. *Wildlife Research* 35: 651–662, <https://doi.org/10.1071/WR07072>
- Dorman DC, Parker AJ, Buck WB (1990) Bromethalin toxicosis in the dog. Part I: clinical effects. Part II: selected treatments for the toxic syndrome. *Journal of the American Animal Hospital Association* 26: 589–594, 595–598
- Dreikorn BA, O'Doherty GOP (1984) The discovery and development of bromethalin, an acute rodenticide with a unique mode of action. *ACS Symposium Series* 255: 45–63, <https://doi.org/10.1021/bk-1984-0255.ch004>
- Eason CT, Murphy EC, Hix S, MacMorran DB (2010) Development of a new humane toxin for predator control in New Zealand. *Integrative Zoology* 5: 31–36, <https://doi.org/10.1111/j.1749-4877.2010.00183.x>
- Eason CT, Miller A, MacMorran DB, Murphy EC (2014) Toxicology and ecotoxicology of para-aminopropiophenone (PAPP) - a new predator control tool for stoats and feral cats in New Zealand. *New Zealand Journal of Ecology* 38: 177–188
- ERMA (2011a) Environmental Risk Management Authority (ERMA). Environmental Risk Management Authority Decision. Application Code HSR09058. ERMA, New Zealand. <https://www.USEPA.govt.nz/assets/FileAPI/hsno-ar/HSR09058/HSR09058-HSR09058-Decision.pdf> (accessed 18 May 2018)
- ERMA (2011b) Environmental Risk Management Authority (ERMA). ERMA New Zealand Evaluation and Review Report. Application for Approval to Import or Manufacture PAPP Paste A, PAPP Paste B and PAPP Ready-to-use Bait for Release. Application Code HSR09058. ERMA, New Zealand. <https://www.USEPA.govt.nz/assets/FileAPI/hsno-ar/HSR09058/HSR09058-HSR09058-E-and-R-Report.pdf> (accessed 18 May 2018)
- Everard COR, Everard JD (1992) Mongoose rabies in the Caribbean. *Annals of the New York Academy of Sciences* 653: 356–366, <https://doi.org/10.1111/j.1749-6632.1992.tb19662.x>
- Everard COR, Green AE, Glosser JW (1976) Leptospirosis in Trinidad and Grenada, with special reference to the mongoose. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 70: 57–61, [https://doi.org/10.1016/0035-9203\(76\)90008-0](https://doi.org/10.1016/0035-9203(76)90008-0)
- Fisher P, O'Connor C, Wright G, Eason CT (2003) Persistence of poor anticoagulant rodenticides in the liver of rats. DOC Science Internal Series 139. Department of Conservation, New Zealand. <https://www.doc.govt.nz/documents/science-and-technical/dsis139.pdf> (accessed 13 August 2018)
- Foster J (2011) Effects of sodium nitrite on feral swine and non-targets. Unpublished final report. TDA Project No. FH-10-05. Texas Department of Agriculture Performance Report, TX.

- Foster JA, Martin JC, VerCauteren KC, Phillips GE, Eisemann JD (2014) Optimization of formulations for the lethal control of feral pigs. In: Timm RM, O'Brien JM (eds), Proceedings of the 26th Vertebrate Pest Conference. University of California, Davis, California, USA, pp 277–280, <https://doi.org/10.5070/V426110652>
- Hays WST, Conant S (2007) Biology and impacts of Pacific Island invasive species. 1. A worldwide review of effects of the Small Indian Mongoose, *Herpestes javanicus* (Carnivora: Herpestidae). *Pacific Sciences* 61: 3–16, <https://doi.org/10.1353/psc.2007.0006>
- IMVS (2010) Institute of Medical and Veterinary Services (IMVS). Assessing the humaneness and efficacy of a new feral pig bait in domestic pigs. Report for the Australian Government Department of the Environment, Water, Heritage and the Arts, Australia. <https://www.environment.gov.au/system/files/resources/091b0583-f35c-40b3-a530-f2e0c307a20c/files/pigs-imvs-report.pdf> (accessed 23 August 2018)
- IUCN (2018) International Union for Conservation of Nature (IUCN), Global Invasive Species Database. 100 of the World's Worst Invasive Alien Species. http://www.iucngisd.org/gisd/100_worst.php (accessed 16 May 2018)
- Jackson WB, Spaulding SR, Van Lier RBL, Dreikorn BA (1982) Bromethalin-A promising new rodenticide. In: Marsh, RE (ed), Proceedings of the Tenth Vertebrate Pest Conference. University of California, Davis, California, USA, pp 10–16
- Landcare Research (2010) How humane are our pest control tools? (09-11326). MAF Biosecurity New Zealand Technical Paper No: 2011/01. Ministry of Agriculture and Forestry, New Zealand. <https://www.mpi.govt.nz/dmsdocument/4009/loggedIn> (accessed 23 August 2018)
- Lapidge SJ, Eason CT (2010) Pharmacokinetics and methaemoglobin reductase activity as determinants of species susceptibility and non-target risks from sodium nitrite manufactured feral pig baits. Report for the Australian Government Department of the Environment, Water, Heritage and the Arts, Australia. <https://www.environment.gov.au/system/files/resources/091b0583-f35c-40b3-a530-f2e0c307a20c/files/pigs-sodium-nitrite-risk-assessment.pdf> (accessed 23 August 2018)
- Keith JO, Hirata DN (1988a) Determination of an acute, oral LD50 for diphacinone against mongooses (*Herpestes auropunctatus*). Unpublished final report. U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Denver Wildlife Research Center, USA
- Keith JO, Hirata DN (1988b) Laboratory trials to determine mortality of mongooses (*Herpestes auropunctatus*) fed 0.00025% diphacinone bait. Unpublished final report. U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Denver Wildlife Research Center, USA
- Keith JO, Espy DL, Hirata DN (1988) Small field efficacy trials using diphacinone bait against mongooses (*Herpestes auropunctatus*). Unpublished final report. U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Denver Wildlife Research Center, USA
- Keith JO, Hirata DN, Espy DL, Greiner S, Griffin D (1989) Field Trials to determine efficacy of diphacinone (0.00025%) bait on controlling mongoose predation of endangered Hawaiian birds. Unpublished final report, QA-16. U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Denver Wildlife Research Center, USA
- Marks CA, Gigliotti F, Busana F, Johnston M, Lindeman M (2004) Fox control using a para-aminopropiophenone formulation with the M-44 ejector. *Animal Welfare* 13: 401–407
- McLeod L, Saunders G (2013) Pesticides used in the management of vertebrate animals in Australia: A review. NSW Government Department of Primary Industries, Australia. https://www.dpi.nsw.gov.au/_data/assets/pdf_file/0007/486187/Pesticides-used-in-the-management-of-vertebrate-pests-in-australia-a-review.pdf (accessed 23 August 2018)
- Neogen Corporation (2012) Rodenticides: Technical product catalog and usage guide. AN198-0912. http://www.hacco.com/other_pdf/rodenticidetechncatalog.pdf (accessed 2 January 2018)
- NZEPA (2013) New Zealand Environmental Protection Authority (NZEPA). Environmental Protection Authority Decision. Application code ERMA200570. <https://www.epa.govt.nz/assets/FileAPI/hsno-ar/ERMA200570/ERMA200570-ERMA200570-Decision-final-web.pdf> (accessed 10 August 2018)
- Pimentel D, Lach L, Zuniga R, Morrison D (2000) Environmental and economic costs of nonindigenous species in the United States. *BioScience* 50: 53–65, [https://doi.org/10.1641/0006-3568\(2000\)050\[0053:EAECON\]2.3.CO;2](https://doi.org/10.1641/0006-3568(2000)050[0053:EAECON]2.3.CO;2)
- Pitt WC, Sugihara RT (2009) Spatial (foraging distance) and temporal (time and frequency of visitation) responses of marked small Indian mongooses (*Herpestes auropunctatus*) to selected food baits in Hawaii. Unpublished final report, QA-1255. U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Wildlife Services, National Wildlife Research Center, Hawaii Field Station. USA
- Pitt WC, Eisemann JD, Swift CE, Sugihara RT, Dengler-Germain B, Driscoll L (2005) Diphacinone residues in free-ranging wild pigs following aerial broadcast of rodenticide bait in Hawaiian forests. Unpublished final report, QA-1077. U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Wildlife Services, National Wildlife Research Center, Hawaii Field Station, USA

- Pitt WC, Sugihara RT, Berentsen AR (2015) Effect of travel distance, home range, and bait on the management of small Indian mongooses, *Herpestes auro-punctatus*. *Biological Invasions* 17: 1743–1759, <https://doi.org/10.1007/s10530-014-0831-x>
- Rubinstein I, Weinberg G (2014) Antidote for bromethalin poisoning. *The Canadian Veterinary Journal* 55: 1185
- Savarie PJ, Pan H-P, Hayes DJ, Roberts JD, Dasch GJ, Felton R, Schafer EW (1983) Comparative acute oral toxicity of para-aminopropiophenone (PAPP) in mammals and birds. *Bulletin of Environmental Contamination and Toxicology* 30: 122–126, <https://doi.org/10.1007/BF01610109>
- Shapiro L, Eason C, Bunt C, Hix S, Aylett P, MacMorran D (2016) Encapsulated sodium nitrite as a new toxicant for possum control in New Zealand. *New Zealand Journal of Ecology* 40: 381–385, <https://doi.org/10.20417/nzjecol.40.36>
- Shapiro L, Blackie H, Arthur D, Ross J, Eason C (2018) Secondary poisoning risk for encapsulated sodium nitrite, a new tool for possum control. *New Zealand Journal of Ecology* 42: 65–73, <https://doi.org/10.20417/nzjecol.42.6>
- Simberloff D (2003) How much information on population biology is needed to manage introduced species? *Conservation Biology* 17: 83–92, <https://doi.org/10.1046/j.1523-1739.2003.02028.x>
- Smith DG, Polhemus JT, VanderWerf EA (2000) Efficacy of fish-flavored diphacinone bait blocks for controlling small Indian mongoose (*Herpestes auro-punctatus*) populations in Hawai'i. *'Elepaio* 60: 47–51
- Snow NP, Foster JA, Kinsey JC, Humphrys ST, Staples LD, Hewitt DG, VerCauteren KC (2017) Development of toxic bait to control invasive wild pigs and reduce damage. *Wildlife Society Bulletin* 41: 256–263, <https://doi.org/10.1002/wsb.775>
- Sugihara RT, Pitt WC, Berentsen AR, Payne CG (2018) Evaluation of the palatability and toxicity of candidate baits and toxicants for mongooses (*Herpestes auro-punctatus*). *European Journal of Wildlife Research* 64: 2, <https://doi.org/10.1007/s10344-017-1163-9>
- USEPA (1998) U.S. Environmental Protection Agency. R.E.D. FACTS. Rodenticide Cluster. USEPA-738-F-98-004. EPA Office of Prevention, Pesticides, and Toxic Substances, USA. <https://archive.epa.gov/pesticides/reregistration/web/pdf/2100fact.pdf> (accessed 23 August 2018)
- USEPA (2008) U.S. Environmental Protection Agency. Risk Mitigation Decision for Ten Rodenticides. EPA Office of Prevention, Pesticides, and Toxic Substances, USA. <https://www.regulations.gov/document?D=EPA-HQ-OPP-2006-0955-0764> (accessed 18 May 2018)
- USEPA (2015) U.S. Environmental Protection Agency. Memorandum. Registration Review-Preliminary Problem Formulation for Ecological Risk and Environmental Fate, Endangered Species, and Drinking Water Assessments for Diphacinone and Diphacinone Sodium Salt. USEPA-HQ-OPP-2015-0777-0005. EPA Office of Pesticide Programs, USA. <https://www.regulations.gov/document?D=EPA-HQ-OPP-2015-0777-0005> (accessed 2 February 2018)
- USEPA (2016a) U.S. Environmental Protection Agency. Memorandum. Problem Formulation for the Environmental Fate, Ecological Risk, and Drinking Water Assessments to be Conducted in Support of the Registration Review for Bromethalin. USEPA-HQ-OPP-2016-0077-0007. EPA Office of Pesticide Programs, USA. <https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0077-0007> (accessed 2 February 2018)
- USEPA (2016b) U.S. Environmental Protection Agency. Memorandum. Rodenticides: Summary of Hazard and Science Policy Council (HASPOC) Meeting on October 1, 2015: Recommendation on Data Requirements for Rodenticides. USEPA-HQ-OPP-2016-0077-0011. EPA Office of Chemical Safety and Pollution Prevention, USA. <https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0077-0011> (accessed 2 February 2018)
- USEPA (2018) U.S. Environmental Protection Agency. DRC-1339 (Starlicide): Preliminary Ecological Risk Assessment for Registration Review. EPA Office of Prevention, Pesticides, and Toxic Substances, USA. <https://www.regulations.gov/document?D=EPA-HQ-OPP-2011-0696-0015> (accessed 12 March 2019)
- USEPA (2019) U.S. Environmental Protection Agency. PRIA 4 Fee Determination Decision Tree. EPA Office of Prevention, Pesticides, and Toxic Substances, USA. <https://www.epa.gov/pria-fees/pria-4-fee-determination-decision-tree> (accessed 14 March 2019)
- USFWS (2011) U.S. Fish and Wildlife Service. Recovery Plan for Hawaiian Waterbirds, Second Revision. USFWS Region 1, USA. https://www.fws.gov/pacificislands/CH_Rules/Hawaiian%20Waterbirds%20RP%202nd%20Revision.pdf (accessed 23 August 2018)
- USFWS (2017) U.S. Fish and Wildlife Service. Summary of Species Listed as Injurious Wildlife under the Lacey Act (18 U.S.C. § 42). https://www.fws.gov/injuriouswildlife/pdf_files/Current_Listed_IW.pdf (accessed 15 May 2018)
- Wong M, Katz AR, Li D, Wilcox BA (2012) Leptospira infection prevalence in small mammal host populations on three Hawaiian islands. *The American Journal of Tropical Medicine and Hygiene* 87: 337–341, <https://doi.org/10.4269/ajtmh.2012.12-0187>
- Zieger U, Marson DA, Sharma R, Chikweto A, Tiwari K, Sayyid M, Lousin B, Goharriz H, Voller K, Breed AC, Werling D, Fooks AR, Horton DL (2014) The phylogeography of rabies in Grenada, West Indies, and implications for control. *PLOS Neglected Tropical Diseases* 8: e3251, <https://doi.org/10.1371/journal.pntd.0003251>