A systematic review of the safety of potassium bromide in dogs

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Objective—To critically evaluate and summarize available information on the safety of potassium bromide in dogs.

Design—Systematic review.

Sample—111 references reporting safety information relevant to potassium bromide published between 1938 and 2011.

Procedures—PubMed searches without date limitations were conducted with the terms "potassium bromide" and "sodium bromide" in December 2009 and October 2011. Additional articles were identified through examination of article reference lists and book chapters on seizures in dogs and pharmacology.

Results—Reversible neurologic signs were the most consistently reported toxicoses and were generally associated with adjunctive potassium bromide treatment or high serum bromide concentrations. Dermatologic and respiratory abnormalities were rare in dogs. Insufficient information was available to assess the effects of potassium bromide on behavior or to determine the incidence of vomiting, weight gain, polyphagia, pancreatitis, polyuria, polydipsia, or reproductive abnormalities associated with potassium bromide administration. Evidence suggested that administration of potassium bromide with food may alleviate gastrointestinal irritation and that monitoring for polyphagia, thyroid hormone abnormalities, and high serum bromide concentrations may be beneficial.

Conclusions and Clinical Relevance—Results suggested that potassium bromide is not an appropriate choice for treatment of every dog with seizures and that practitioners should tailor therapeutic regimens and clinical monitoring to each dog. Abrupt dietary changes or fluid therapy may compromise seizure control or increase the likelihood of adverse events. Availability of an appropriately labeled, approved potassium bromide product could provide better assurance for veterinarians and their clients of the quality, safety, and effectiveness of the product for veterinary use. (*J Am Vet Med Assoc* 2012;240:705–715)

Potassium bromide was first reported as a treatment for epilepsy in people in 1857[1] and was described as an animal treatment before 1876.[2] The drug was widely available over the counter during the early part of the 20th century, and in 1938, sales of products containing bromide in the United States were second only to sales of products containing acetylsalicylic acid.[3] Although bromide salts are still used to treat specific types of refractory seizures in children,[4,5] the use of KBr in humans has decreased throughout the 20th century owing to the availability of other antiseizure medications that have fewer toxic effects.[6] Undesirable effects of bromides in humans include lethargy, sleepiness, confusion, hallucinations, muscle pain, ataxia, nausea, vomiting, anorexia, acneiform and erythematous rashes, nodular and pustular skin lesions, stupor, and coma.[3,7]

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Abbreviations

ADE	Adverse drug event
GI	Gastrointestinal
KBr	Potassium bromide
NaBr	Sodium bromide
PB	Phenobarbital
PD	Polydipsia
PU	Polyuria

In dogs, PB and KBr are still considered the standard treatment for long-term management of seizures associated with idiopathic epilepsy,[8–10] the most common neurologic disorder in dogs.[9] In a recent Australian survey,[11] 80% of veterinarians reported that they used KBr to manage seizures in dogs. Although KBr has traditionally been used in combination with PB, it is increasingly being used as a single agent for treatment of dogs with seizures[12–14] and it has been recommended as a first-line anticonvulsant in some dogs with newly diagnosed epilepsy.[8,14] Concern regarding serious ADEs associated with PB, such as pancytopenia[15] and hepatotoxicosis,[16] and the restrictions associated with dispensing PB related to its classification as a controlled substance also make KBr a more convenient choice than PB for seizure management.[17]

Potassium bromide and, to a lesser extent, NaBr are compounded and marketed in the United States as a solution or in capsules. Potassium bromide, NaBr, and PB have not been approved by the US FDA for use in humans or animals in the United States. This means that these drugs have not been reviewed by the FDA to determine whether they are safe and effective or to show that they are produced in a consistent manner according to recognized quality standards. For unapproved drugs, there is no mandatory requirement for reporting of ADEs by drug manufacturers; therefore, the FDA Center for Veterinary Medicine receives relatively few ADE reports related to these products. Without FDA approval and mandatory ADE reporting, the safety, effectiveness, and quality of KBr products available to practitioners and patients in the United States cannot be ensured, potentially leaving veterinarians and pet owners unaware of adverse effects and other risks involved with the use of KBr. Because KBr is commonly used in the veterinary community, it is important that veterinarians have the information necessary to prescribe it in the safest manner possible. The purpose of the study reported here was to systematically review and critically evaluate the published literature on the safety of KBr in dogs.

Materials and Methods

A PubMed search was conducted in December 2009 with the term "potassium bromide" to identify articles related to the safety of bromide. Additional articles were identified through manually searching reference lists in the identified publications, in other relevant articles, and in book chapters on seizures in dogs and pharmacology. The literature search was repeated in October 2011, adding the term "sodium bromide," to identify articles that had been published following the original PubMed search and to more completely encompass potential adverse effects expected with KBr treatment because the initial search identified information relevant to KBr safety in articles reporting results of studies that used NaBr.

Published reports that did not involve systemic administration of bromides to humans or animals or did not assess physiologic effects were excluded because they were not applicable to this review. Individual reports were not excluded on the basis of study design, species of interest, condition being treated, or language of publication. Foreign language references were evaluated first on the basis of the title and then on the basis of a review of the abstract; references that appeared potentially relevant on the basis of the title or abstract were translated into English.

Potentially relevant publications were reviewed to determine the physiologic systems involved and the strength of evidence linking each reported ADE to KBr or NaBr. Review and historical articles with no original data and reports of bromide use in humans or dogs in which toxicity was not examined were excluded. Relationships among treatment groups were examined, the evidence was evaluated for causality of adverse events, and it was determined whether findings were statistically significant. Articles were classified as providing primary, supportive, or anecdotal evidence on the basis of an evaluation of the strength of evidence presented in the article, as described.[18] Publications that contained quantitative or descriptive data investigating adverse effects of bromide treatment in mammals were considered to provide primary evidence. Publications reporting studies in which safety monitoring was conducted but no ADEs were seen were also considered to provide primary evidence. Publications in which ADEs were described in the context of a study, but without data, and publications that discussed important ADEs but lacked sufficient case detail to definitively attribute the reported ADEs to KBr or NaBr administration were considered to provide supportive evidence. Publications were classified as providing anecdotal evidence if they contained opinions or observations by experts rather than objective, supportive safety data. The strength of evidence available in each article was summarized, and spreadsheet templates were used to organize reports of bromide-associated toxicoses by specific body systems. Findings were summarized by system; additional literature on physiologic mechanisms was incorporated to provide interpretive context.

Results

The PubMed searches retrieved 843 publications. Searches of reference lists in these articles and in book chapters and additional targeted searches yielded 93 additional publications, resulting in a total database of 936 publications. Of these, 703 were eliminated because they did not discuss systemic use of KBr or did not contain physiologic information or because bromide was used only to measure the extracellular water compartment. Of the 233 remaining publications, 38 were in a foreign language. Of these, 20 had English titles or abstracts that appeared relevant and were translated. Eight of these 20 were included in the systematic review.[19–26] Twelve translated articles and 12 other foreign-language publications that could be evaluated without translation on the basis of their titles, abstracts, tables, or figures were found to lack sufficient specific data on ADEs associated with bromides. Six other foreign-language publications were not translated because they were judged to provide information similar to information that had already been reviewed. These 30 publications were not included in the review.

Publications that discussed the use of bromide as a treatment in humans or animals included 42 historical or review articles that contained only descriptive summaries and no original data. Another group of publications discussed use of bromides in humans (n = 14), horses (2), rats (4), or chicks (1), but no ADEs were reported. It was unclear in these 21 publications whether ADEs were not evaluated, were not reported, or were truly not observed. In 22 other publications, KBr was used in dogs but no ADEs could be directly attributed to bromide administration. In these publications, there was insufficient description to determine whether ADEs were evaluated at all or were not observed, affected animals had other treatments or conditions likely to produce observed signs, physiologic measurements were described but no clinical changes were observed, or the provided information was vague and the types of ADEs described were documented in other references containing data. Seven publications reported findings only in nonmammalian species, including flies, fish, and birds. Although these 92 publications did not provide data for assessing bromide toxicity, some of them provided background and contextual information that was used in the descriptive review.

The 111 publications that provided data on drug safety included those in which KBr or NaBr was used

as a monotherapy or as a part of combination treatment (usually with PB). There were few controlled trials involving dogs that evaluated the safety of KBr when used alone; however, there were many reports of observational studies. On the basis of our critical review, 38 publications provided primary evidence relevant to KBr safety (**Table 1**); these publications contained data related to dogs,[15,27–37,a] cats,[38,39] rats,[40–49] mice,[50,51] cat-

Table 1—Characteristics of 38 publications that provided primary evidence regarding adverse effects of KBr relevant for dogs.

Author	Year	Species	No. treated	Drug	Study design	Body system affected and signs
Bel et al[54]	2001	Humans	1	NaBr	Case report	Dermatologic (vegetative skin lesions)
Boothe[a]	2002	Dogs	23	KBr	Randomized controlled trial	Neurologic (ataxia, obtundation, hyperactivity, and abnormal behaviors), GI (vomiting, polyphagia, and 10% weight increase), and PU and PD
Boothe et al[38]	2002	Cats	17	KBr	Cross-sectional study	GI (vomiting and weight gain), PU and PD, and respiratory (coughing and bronchial asthmatic changes)
Boothe et al[38]	2002	Cats	7	KBr	Experimental study	No ADEs reported during observation period
Buchberger et al[40]	1990	Rats	36	NaBr	Experimental study	Neurologic (hypoactivity), GI (decreased weight and anorexia), dermatologic (ruffled fur), endocrine (decreased thyroxine and triiodothyronine and increased thyroid-stimulating hormone concentrations), and death
Chang et al[27]	2006	Dogs	4	KBr	Cross-sectional survey	Neurologic (lethargy, ataxia, and restlessness), GI (vomiting, diarrhea, and polyphagia), and dermatologic (pruritus)
Diener et al[55]	1998	Humans	5	KBr	Case series	GI (vomiting and diarrhea), pancreatitis, dermatologic (folliculitis, subcutaneous nodules, and necrotizing panniculitis), and fever
Disse et al[41]	1996	Rats	18	NaBr	Experimental study	Reproductive (in offspring of treated dams: lower body and brain weight, delayed behavioral development, and modified neuroplasticity)
Genicot et al[19]	1991	Cattle	11	KBr	Experimental study	GI (polyphagia and lower weight gain compared with controls)
Goldstein[50]	1979	Mice	30	NaBr	Experimental study	Neurologic (sedation, loss of righting reflex, and ataxia) and death
Hafiji et al[56]	2008	Humans	1	Pipobroman (bromide-containing drug)	Case report	Neurologic (delusions, hallucinations, and depression) and dermatologic (erythematous, papulonodular eruption with erosions, pustules, and necrosis)
Hanes and Yates[3]	1938	Humans	400	Bromide	Case series	Neurologic (headache, delusions, emotional changes, lethargy, memory loss, and ataxia), dermatologic (rash and papules), and reproductive (loss of libido)
Hansen and Hubner[51]	1983	Mice	100	NaBr	Experimental study	Neurologic (restlessness and behavioral changes) and GI (weight loss)
Harned et al[42]	1944	Rats	97	NaBr	Experimental study	Reproductive (in offspring of treated dams: stillbirths, neonatal deaths, delayed growth, and slower maze learning)
Harris and Derian[28]	1949	Dogs	3	NaBr	Experimental study	Neurologic (lethargy and incoordination), GI (diarrhea and oral ulceration), and dermatologic (pustular dermatitis)
Jacobs et al[15]	1998	Dogs	1	KBr and clorazepate dipotassium	Case series	No ADEs reported during 8-week follow-up period
			2	PB		
Kagitani-Shimono et al[57]	2005	Humans	4	NaBr	Case series	No ADEs reported during 2- to 5-year follow-up period
Kantrowitz et al[29]	1999	Dogs	8	KBr	Cross-sectional study	Endocrine (no thyroid hormone changes among dogs treated with KBr alone)
			15	KBr and PB		
			55	PB		
Knight and Reina-Guerra[52]	1977	Cattle	14	NaBr	Experimental study	Neurologic (ataxia)
Loeber et al[43]	1983	Rats	50	NaBr	Experimental study	Endocrine (decreased thyroxine and growth hormone concentrations and decreased growth) and reproductive (decreased spermatogenesis)
March et al[30]	2002	Dogs	6	KBr	Experimental study	Neurologic (caudal paresis, ataxia, hyporeflexia, and agitation)
Millikan and Paul[58]	1946	Humans	36	NaBr	Uncontrolled clinical trial	Neurologic (sleepiness, ataxia, slurred speech, grogginess, disorientation, and hallucinations) and GI (nausea and vomiting)
Newsome et al[44]	1978	Rats	20	NaBr	Experimental study	Endocrine (increased thyroxine concentration) and GI (no anorexia and possibly decreased growth)
Palmer and Clarke[31]	1933	Dogs	2	NaBr	Experimental study	No ADEs reported during observation period
Paull et al[32]	2003	Dogs	5	KBr	Experimental study	Endocrine (no thyroid hormone changes); no ADEs reported during 6-month follow-up period

Table 1 continued—Characteristics of 38 publications that provided primary evidence regarding adverse effects of KBr relevant for dogs.

Author	Year	Species	No. treated	Drug	Study design	Body system affected and signs
Perkins[59]	1950	Humans	27	Various bromides	Case reports	Neurologic (paresis, ataxia, tremor, hallucinations, disorientation, sleepiness, headache, muscle pain, hyporeflexia or hyperreflexia, anisocoria, depression, irritability, stupor, coma, and increased CSF total protein concentration), GI (stomach cramps, foul breath), dermatologic (rash), fever, and death
Raidal and Edwards[53]	2008	Horses	12	KBr	Experimental study	Neurologic (ataxia and proprioceptive deficits)
Rosenblum[33]	1958	Dogs	24	NaBr	Experimental study	Neurologic (ataxia, stupor, shivering, and coma), GI (salivation, weight loss, vomiting, and diarrhea), dermatologic (nonsuppurative, macular, and scaly dermatitis), and death
Rossmeisl and Inzana[34]	2009	Dogs	31	KBr or KBr and PB	Case-control study	Neurologic (paresis, ataxia, mydriasis, aggression, stupor, and coma) and GI (regurgitation and megaesophagus)
			52	None (epileptic controls)		
Sangster[60]	1983	Humans	24	KBr	Experimental study	Neurologic (sleepiness and grogginess), GI (nausea), and endocrine (increased thyroxine and triiodothyronine concentrations)
Steiner et al[35]	2008	Dogs	98	KBr	Cross-sectional study	Pancreatitis (no evidence for ADEs on the basis of canine pancreatic lipase immunoreativity)
			118	PB		
			121	KBr and PB		
Schwartz et al[36]	2011	Dogs	1	KBr	Case report	No ADEs reported during 8-week follow-up period
van Leeuwen et al[45]	1983	Rats	500	NaBr	Experimental study	Reproductive (male and female infertility, fewer offspring, and postnatal death) and endocrine (decreased thyroxine and increased thyroid-stimulating hormone concentrations)
van Logten et al[46]	1973	Rats	16	NaBr	Experimental study	Neurologic (incoordination and decreased grooming)
van Logten et al[47]	1974	Rats	100	NaBr	Experimental study	Neurologic (incoordination and decreased grooming), endocrine (growth retardation), and reproductive (decreased spermatogenesis and fewer corpora lutea)
Velický et al[48]	1997	Rats	120	KBr	Experimental study	Endocrine (decreased thyroxine and triiodothyronine concentrations and parenchymatous goiter-like changes in thyroid gland)
Vobecký et al[49]	2005	Rats	10 dams and 80 pups	KBr	Experimental study	Reproductive (decreased survival of young, retarded growth, and decreased milk production) and GI (anorexia and weight loss)
Wagner[39]	2001	Cats	26	KBr	Cohort study	Respiratory (cough and severe dyspnea) and death
Yohn et al[37]	1992	Dogs	1	KBr	Case report	Neurologic (depression, stupor, hyporeflexia, anisocoria, paresis, and muscle pain)

tle,[19,52] horses,[53] and humans.[54–60] Among these 38 publications providing primary evidence, there were 22 experimental studies (5 involving dogs and 17 involving other species), 2 clinical trials (1 involving dogs and 1 involving humans), 1 cohort study involving cats, 1 case-control study involving dogs, 4 cross-sectional studies (3 involving dogs and 1 involving cats), and 9 case reports or case series (3 involving dogs and 6 involving other species). One publication included data from 2 types of studies.

Sixty publications were classified as providing supportive evidence, such as descriptive information that supported ADEs documented in the primary evidence publications. These publications involved dogs,[13,17,20,61–74,b,c] cats,[21] rabbits,[22,61] rats,[75–82] mice,[83] cattle,[84] goats,[84,85] horses,[84,86] and humans.[5,7,23,24,87–109] These publications described important ADEs, but were limited in their ability to clearly attribute ADEs to bromide administration. Some publications evaluated KBr only when administered in combination with PB or other anticonvulsant drugs. Some patients had concurrent diseases or complex medical histories, making it difficult to determine whether clinical signs could be attributed to bromide administration. Other publications loosely described bromism or general signs, but did not provide quantitative data.

Thirteen publications were considered to provide anecdotal evidence. These included 5 letters to the editor discussing publications that had already been examined,[26,110–113] 5 brief reports that provided comments about adverse effects but did not provide data,[25,114–117] and 3 abstracts of presentations that described preliminary results from small studies involving KBr administration but did not mention whether adverse events were identified.[d–f]

On the basis of the identified publications, body systems for which ADEs were reported included the neurologic (including behavioral), GI (including pancreatitis), reproductive, endocrine, dermatologic, and respiratory systems. Additionally, PU and PD were frequently mentioned; however, these were considered to be relatively nonspecific signs and were not associated with a single body system.

Discussion

Evaluation of the safety of a new animal drug is a critical part of the FDA drug approval process. Preapproval assessment of potential ADEs is generally based on preliminary data about the structure and pharmacology of the compound, experimental studies, and observations from clinical trials.[118] This information is used to predict safety for the larger population of animals that will be treated if the drug is approved and marketed. For drugs such as KBr, which have already been widely used in animal populations, information on health effects with clinical use can be directly observed, rather than relying solely on inference from experimental studies. However, the number of published articles that directly address safety questions may be limited. In the present study, we identified a considerable body of pharmacological, primary, and supportive evidence regarding the in vivo safety of KBr.

Potassium bromide is a halide salt that is thought to exert its antiepileptic activity by passing through neuronal chloride ion channels, thereby hyperpolarizing neuronal membranes, raising the seizure threshold, and stabilizing neurons against excitatory input from epileptic foci.[12] Bromide ions have a smaller hydrated diameter than chloride ions do and therefore passively cross these neuronal channels more readily.[7] Bromide distributes into the CSF and interstitial tissues of the brain and is actively transported out of the CNS via the choroid plexus. At pharmacological doses, the active transport mechanism is overwhelmed and bromide accumulates in the brain and CSF.[12]

When given orally as NaBr, the estimated bioavailability of bromide in dogs is 46%,[119] but bioavailability may differ considerably among individuals. Generally, KBr and NaBr solutions would be expected to have similar GI absorption, although because of molecular weight differences, a solution of 250 mg of KBr/mL would be equivalent to a solution of 211 mg of NaBr/mL. The prandial state of the animal would not be expected to affect bromide absorption because bromide is water soluble and absorbed along the entire GI tract.[120] Corn syrup or flavored sweeteners have been added to compounded bromide solutions to improve palatability.[121] The addition of low-digestible carbohydrates, such as mannitol and sorbitol, may alter the osmolarity of intestinal fluids and result in changes to the rate of GI transit.[122]

Bromide is not subject to hepatic metabolism, making it suitable for use in dogs with hepatic disease.[9,123] It is excreted unchanged by the kidneys, where it is freely filtered by the glomeruli and then undergoes tubular reabsorption in competition with chloride.[62] Bromide is reabsorbed more readily than is chloride[119] and distributes throughout the body, essentially replacing chloride in body fluids.[120] Therefore, the reported mean volume of distribution of 0.45 L/kg (0.20 L/lb) approximates the extracellular fluid space.[12] The mean elimination half-life of bromide when KBr is orally administered to dogs has been estimated to be from 24.9[124] to 46 days.[119] Dietary chloride has been shown to be a key variable affecting the elimination half-life of bromide.[125] Generally, regular administration of KBr for 4 to 5 half-lives is required for serum bromide concentrations to reach steady state. Therapeutic serum bromide concentrations may be achieved more quickly by administration of loading doses of KBr.

Animals with decreased renal function may be predisposed to bromide toxicosis owing to a decreased ability to eliminate bromide as a result of reduced glomerular filtration rate.[34,65] Increased chloride intake leads to increased urinary elimination of bromide,[9] likely as a result of competition for tubular reabsorption between chloride and bromide.[125] Trepanier and Babish[125] found that an increase in dietary chloride content from 0.2% to 1.3% led to a decrease in serum bromide half-life from 69 to 24 days. They also found that, among 11 commercial dry dog foods, chloride content ranged from 0.33% to 1.32% on a dry-matter basis. Abrupt diet changes in dogs receiving KBr could either compromise seizure control or raise safety concerns.[72] Use of IV fluids containing chloride could also reduce serum bromide concentration to subtherapeutic concentrations during fluid therapy.[10] Loop diuretics, such as ethacrynic acid and presumably furosemide, may also increase bromide elimination by blocking chloride and bromide reuptake.[65] It has also been suggested, albeit anecdotally, that NaBr rather than KBr should be used in patients with adrenal insufficiency because these patients may have difficulty maintaining potassium homeostasis.[123] Because of factors affecting the dose-response relationships for KBr, treatment is generally titrated to effect for individual dogs.[69]

Given the pharmacological properties of bromide and specific information in the 111 publications identified in the present study, the effects of KBr could be summarized for multiple physiologic systems. Bromide toxicosis in dogs was most frequently associated with high serum bromide concentrations; however, authors have reported that toxicoses can be seen at low concentration in unusually sensitive dogs.[30,33] One study[126] found that most dogs that develop signs of toxicoses with bromide monotherapy had serum bromide concentrations in the range of 2.4 to 4 mg/mL but also found that dogs were successfully treated without signs of toxicoses at serum concentrations as high as 4 to 4.8 mg/mL. Another publication[30] reported clinical signs of toxicosis at serum bromide concentrations of approximately 4 mg/mL, but no signs of toxicoses at concentrations of 1.78 to 2.7 mg/mL.[30] In a laboratory study,[33] unspecified minimal signs of toxicosis were found in dogs given 100 mg of NaBr/kg/d (45.5 mg/lb/d) for 6 weeks; mean serum concentration was 2.7 mg/mL. However, in the same study, 3 deaths occurred between weeks 4 and 6 in another group of dogs treated with 200 mg of NaBr/kg/d (90.9 mg/lb/d). The importance of monitoring clinical signs for individual animals should be emphasized because effective and toxic serum bromide concentrations have been reported to differ between dogs[34] and an overlap in toxic versus nontoxic serum concentrations has been demonstrated. In fact, the use of clinical signs to judge appropriateness of treatment may be more important than monitoring serum bromide concentration alone.

Neurologic and behavioral signs were the most commonly reported ADEs associated with bromide ad-

ministration in dogs and other species in clinical and experimental studies reviewed in the present study. Sedation and, conversely, irritability and restlessness have been reported in dogs[3,8,27–31,a,c] and humans.[3,22] A sedative, calming effect has also been reported in horses.[127] Cattle treated with KBr had a decrease in aggressive behavior, compared with untreated controls.[19] Signs of more severe bromism were also similar across species and included signs of depression,[56] behavioral changes,[40,50,51,58] ataxia,[27,28,33,34,50,52,53,58,a,c] hind limb paresis,[30,31,35] mydriasis,[34,35,37,59] stupor,[59] and coma.[33,34,59,65,69] In humans, headache,[3,59] sleepiness,[58–60] muscle pain,[37,59] and hallucinations[56,58] have also been reported. Neurologic signs have been described when KBr was used alone or in addition to PB.[30,34,37,65,b] In clinical studies, observed behavioral changes could also stem from the prodromal or postictal phases of seizure activity rather than from bromide toxicosis.[128] Adverse neurologic effects are reversible and may be alleviated within several days by decreasing the PB dose by 10% to 30% (when bromide is given in combination with PB) and within hours by treating with saline (0.9% NaCl) solution IV.[12,37,65,113,121]

Gastrointestinal ADEs have also been reported. Vomiting has been commonly described as an adverse effect of both KBr and NaBr administration, but a large number of the reports identified in the present study were anecdotal and lacked supportive data. Vomiting was seen in 2 of 20 dogs receiving 400 to 500 mg of NaBr/kg/d (181.8 to 227.3 mg/lb/d) with food.[33] The vomiting in one of those dogs was so severe that drug administration was discontinued. Another study[30] found that KBr at dosages as high as 30 mg/kg (13.6 mg/lb), PO, every 12 hours for 115 days with food did not result in vomiting. Occasional vomiting was reported in the medical histories of 2 of 22 dogs following KBr treatment; however, these dogs were also receiving PB.[74] Vomiting was reported in 1 of 17 cats receiving KBr.[38] Nausea and vomiting have also been reported occasionally for human patients being treated with bromides.[55,58–60] In dogs, transient diarrhea and bloody feces were seen in an experimental study[33] when serum bromide concentrations were 1.8 to 4 mg/mL, but it was unclear how frequently and in how many dogs diarrhea occurred. Three dogs treated with 0.2 g of NaBr/kg/d (0.09 g/lb/d) developed severe, intermittently bloody diarrhea, of which 2 developed oral ulcerations.[28] Diarrhea has also been occasionally reported with clinical use in dogs[27] and humans,[4,55] as have other GI problems. Two reviews anecdotally mentioned megaesophagus as a potential adverse effect of KBr treatment in dogs.[9,34] These adverse GI effects have rarely been severe enough to require cessation of KBr treatment in any species. Potassium bromide and NaBr have long been reported, albeit anecdotally, as gastric irritants, and vomiting has been attributed to this irritant effect.[12,33,34,38,63,121] Administration with food or as a divided dose may be effective in preventing GI irritation.[12,30,58,121] For publications identified in the present study, adverse GI effects could not be clearly attributed to KBr administration, although there was anecdotal support.

Weight loss leading to emaciation has been seen experimentally in rodents[40,49,51,57] and in 10 of 20 dogs receiving large doses of NaBr with controlled caloric intake.[33] Weight gain was seen in 1 of 17 client-owned cats being treated with KBr.[38] In a 221-day study of 22 Belgian White and Blue Cattle (11 of which were treated with KBr), average daily gain was significantly less in KBr-treated animals, compared with untreated animals, in the first 53 days, but time spent eating was significantly increased in the treated animals from days 168 to 221.[19] Polyphagia, a commonly reported adverse effect of both PB and KBr, has been suggested to be a result of increased caloric need or a behavioral effect and may be involved in these weight changes. In most publications that reported polyphagia in the present study, it was difficult to distinguish whether this was actually related to KBr treatment because there was concurrent administration of other drugs. In 1 study,[69] polyphagia was reported in 7 of 23 dogs following the addition of KBr to PB treatment. Given that all of these dogs continued to receive PB, it was unclear whether the polyphagia was due to KBr alone or to the combination of drugs. In a small study,[27] polyphagia was reported by owners of 1 of 4 dogs receiving KBr monotherapy, 6 of 11 dogs receiving PB monotherapy, and 8 of 10 dogs receiving both KBr and PB. On the basis of publications identified in the present study, monitoring food consumption and weight patterns may be warranted in dogs receiving KBr treatment, particularly because polyphagia can lead to garbage ingestion and other complications.[69]

Most KBr-related studies in dogs have not assessed pancreatic outcomes; however, several small studies have explored a possible association between pancreatitis and treatment with a combination of PB and KBr. Schwartz-Porsche and Jurgens[20] reported clinical signs of pancreatitis in 2 of 22 dogs and pancreatic fibrosis at necropsy in 2 of 7 dogs receiving KBr. However, there was no comparison group of untreated dogs and all dogs had previously been treated with maximal doses of either PB or primidone. Hess et al[129] reported pancreatitis to be more common in dogs with epilepsy, although no treatments were compared. Gaskill and Cribb[63] reported that pancreatitis developed in 3 of 6 dogs after KBr was added to PB treatment. They also found, using serum samples from private practices submitted for KBr or PB testing to a diagnostic laboratory, that a higher percentage of dogs with measurable serum concentrations of bromide and PB (10/17) also had high serum amylase or lipase activities, compared with dogs with only measurable PB concentrations (8/88). A history supportive of pancreatitis was reported for a higher percentage of the dogs with measurable serum bromide and PB concentrations (5/17), compared with dogs with only PB concentrations (2/88). Steiner et al[35] used a similar approach with 121 serum samples submitted for KBr or PB testing to relate serum and PB concentrations and canine pancreatic lipase immunoreactivity. There were no significant differences in proportions of dogs with canine pancreatic lipase immunoreactivity > 102.1 µg/L (ie, dogs with canine pancreatic lipase immunoreactivity greater than the upper reference limit) or > 199.9 µ/L (ie, dogs with canine pancreatic lipase immunoreactivity diagnostic for pancreatitis) for dogs with measurable serum concentrations of only bromide, only PB, or both bromide and PB. Interpretation of results from studies that use diagnostic laboratory sub-

missions is difficult because of biases associated with ascertaining exposure and disease status for this type of convenience sample. Additionally, practitioners may be more likely to submit samples from dogs with poor seizure control, signs of toxicosis, or health problems than from otherwise healthy dogs with well-regulated epilepsy. Pancreatitis has been associated with a large number of other drugs in humans, but not with KBr or PB,[130] although it has been mentioned in some case reports.[55] However, pancreatitis in dogs has been associated with abnormal food consumption[131] and polyphagia has been reported for dogs treated with PB, KBr, or a combination of both.[27] Two dogs with pancreatitis were described in a study[69] of 23 dogs, but pancreatitis was attributed to polyphagia and garbage ingestion. Additionally, the clinical signs of pancreatitis (vomiting, lethargy, diarrhea, and signs of abdominal pain)[129] have been individually reported as ADEs, making identification of pancreatitis more complicated. On the basis of our literature review, there was not enough evidence to determine whether dogs receiving KBr were at higher risk of developing pancreatitis.

None of the identified publications in the present study directly assessed the safety of bromide in reproductively active dogs. In humans, reversible impotence and loss of libido were among the first recognized effects of bromides.[1,3] Reversible decreases in fertility have been reported in both female and male rats at NaBr doses ≥ 4,800 mg/kg (2,181.8 mg/lb),[43,45,47] but fetal viability was not affected at dosages of up to 1,200 mg of NaBr/kg/d (545.5 mg/lb/d). Bromide crosses the placenta and is excreted in milk.[49] In rats, gestational treatment of dams led to decreased survival time, lower weight gain, and postnatal developmental delays in offspring.[41,49] Even at lower dosages of 120 mg of NaBr/kg/d (54.5 mg/lb/d) during gestation, offspring had a slower rate of maze learning than did controls.[42] Given the variety of reproductive effects seen in other species, more research is needed to determine whether KBr can be safely used in reproductively active dogs. In general, reproductive effects may be of lesser concern because it is usually recommended that dogs with idiopathic epilepsy be neutered.

Delayed growth was also reported in studies[41–43,47,49] of rats that were exposed as juveniles, but not in utero, and small studies reported other effects potentially related to cellular replication. Six dogs treated with NaBr were described as having delayed callus formation following induced fractures, compared with controls in a Russian study[25] in the 1950s. A study on rabbits[22] and another on rats[47] reported that animals treated with NaBr had lower erythrocyte counts than did controls. These effects have not been reported in other studies; further information is needed to determine whether these findings have relevance for clinical use of KBr.

Therapeutic administration of KBr in dogs was not found to affect thyroid weight or serum total thyroxine, free thyroxine, triiodothyronine, and thyroid-stimulating hormone concentrations or to cause histologic changes.[29,32] In rats and humans, effects have not been reported at therapeutic doses,[43,60] but the thyroid has been identified as a target organ at higher doses. Changes in goitrogenic cellular amounts, identified on the basis of light and electron microscopic evaluation of thyroid tissue, were reported in rats receiving 10, 50, 100, 200, and 400 mg of bromide (as KBr) for various durations.[48,80–82] At very high doses (19,200 mg of NaBr/kg of feed [8,727.3 mg/lb of feed]), histologic changes in rat thyroid tissue (eg, increased number of smaller follicles, higher amounts of follicular epithelium, decreased amounts of colloid, and a more granular appearance) and reduced thyroxine concentration indicated decreased thyroid activity.[43] A statistically significant decrease in total thyroxine concentration was also identified in animals treated in another study[45] with similar design at doses ≥ 4,800 mg/kg. In humans, a bromide intake of 9 mg/kg (4.1 mg/lb) led to increases in serum thyroxine and triiodothyronine concentrations in females, although individual serum concentrations remained within reference limits for the duration of the study.[60] Similar changes were not observed in male subjects or in any subjects treated with 4 mg of bromide/kg (1.8 mg/lb). No precise mechanism of action has been identified; however, effects on transport and perhaps synthesis of thyroid hormones caused by bromide inhibition of active iodide absorption by the thyroid gland have been suggested.[32] Although no effects of KBr on the thyroid gland have been reported for dogs, monitoring serum thyroid hormone concentrations and evaluating thyroid tissues at necropsy would be helpful because available dog studies were small in size.

Polyuria and PD have been reported with clinical use of KBr in dogs. Polyuria and PD were documented in 13 of 23 dogs when KBr was added to PB treatment.[69] In a randomized, controlled trial[a] of 43 epileptic dogs treated with either KBr or PB monotherapy, dogs in both groups developed PU and PD after 1 month of treatment. By 6 months, dogs treated with PB reportedly no longer had PU or PD; none of the dogs treated with KBr had PU, but PD was still present in 4% of these dogs.[a] In a cross-sectional client survey,[27] PU and PD were not described by owners of the 4 dogs receiving KBr monotherapy, but were reported for more than half of the 11 dogs treated with PB and for all 10 dogs treated with both KBr and PB. Polydipsia has also been reported in a cat treated with KBr.[38] This limited and conflicting information makes it difficult to draw conclusions about the relationship between KBr administration and PU and PD.

Skin lesions were rarely reported in experimental overdose studies or in summaries of clinical cases of bromide intoxication in dogs identified in the present study. When reported, skin lesions in dogs were described as nonsuppurative white macules with scales[33] or as pustular dermatitis.[28] Pruritic skin lesions were anecdotally listed as an occasional adverse effect in dogs in 2 reviews.[9,121] In a survey, owners reported pruritus in 1 of 4 dogs treated with KBr; however, no skin changes were described.[27] Skin lesions were not commonly reported in rats but, when observed, were ascribed to poor grooming secondary to neurologic effects.[46,47] In a report[3] of 400 human cases of bromism, cutaneous lesions were a relatively common adverse effect and have been reported in other studies.[5,54–56,59,95] Lesions reported in human cases include acne, bromoderma tuberosum, bromoderma nodosum, and necro-

tizing panniculitis. These lesions may be accompanied by fever, joint and muscle pain, and atrophy of subcutaneous fat.[55] The mechanisms are unknown, but dermatologic lesions have been attributed to both allergic and toxic reactions to accumulated bromide.[56] Overall, dermatologic reactions are not expected to be a problem with clinical KBr use in dogs because of the very small number of cases reported to date.

Respiratory problems were not reported in clinical or toxicity studies in dogs or humans identified in the present study. One author[62] mentioned, as part of a review chapter, that he had encountered several cases of coughing in dogs being treated with KBr. In cats, coughing and dyspnea are a major concern and have been reported following KBr treatment. In 1 study,[38] 6 of 17 cats developed coughing during KBr treatment and 1 had a severe bronchial lung pattern on thoracic radiographs. Sarkisov,[21] in the 1950s, reported that 14 cats treated with NaBr recovered less completely from experimentally induced bacterial pneumonia than did 15 control cats. Treated cats had a clinically prolonged course and developed histologic changes, including thickened bronchiolar walls, alveolar exudate, and emphysema. In another study,[39] 11 of 26 cats treated clinically with KBr developed coughing and dyspnea. Two of these cats treated continuously with KBr had severe signs for several months and subsequently died. High eosinophil counts were present in bronchoalveolar lavage samples collected from 2 of the 11 cats. Feline bronchial asthma, one of the most commonly diagnosed respiratory conditions of cats, is traditionally associated with eosinophilic infiltration.[132] Eosinophils preferentially use bromide to form oxidants that can cause cytotoxicosis, despite low serum bromide concentrations.[133] Studies have not examined the effects of high serum bromide concentrations on eosinophil function. Although the literature supports a concern for KBr administration and respiratory disease in cats, adverse respiratory effects are not expected in dogs on the basis of publications reviewed in the present study.

In the present study, we were able to identify a substantial number of publications providing information relevant to evaluation of the safety of KBr in dogs. The publications that provided primary evidence for this review followed > 170 dogs treated with KBr or NaBr and > 210 dogs treated with KBr combined with PB. However, many of these studies were relatively small, and there was a lack of large randomized, experimental or clinical trials that compared KBr administered alone with a placebo or an active control. Generally, randomized controlled trials and experimental laboratory studies provide the strongest evidence of drug effects.[18] In these types of studies, individuals are randomly assigned to treatment groups to minimize bias and subjects are more intensively monitored for adverse events during the study period.[134] This makes attribution of effectiveness and ADEs of a particular drug much clearer. Randomized trials may also provide information about the frequency of particular ADEs and their relative importance in the study population. However, a limitation of these studies is that results may not reflect or predict how the drug will behave in a more diverse or less healthy general population.[135] Additionally, adverse events that are rare or do not develop in the short period of the clinical trial may not be recognized.[134] Drawing on a full range of publications and including smaller nonrandomized or observational studies may avoid information loss and biases that occur in systematic reviews that use strict exclusion criteria.[136] A number of reviews of human drugs have found that case reports and spontaneous reporting systems provide better information than do clinical trials about new and unexpected ADEs.[137,138] Therefore, the consistency, quality, and quantity of the evidence were evaluated in each article that dealt with safety issues related to KBr, rather than excluding studies on the basis of the type of study design. Important safety information was found in studies of all types. Case studies,[7,13,15,36,37,63,65,84] for example, provided valuable specifics for several kinds of ADEs not reported in other study types.

The present systematic literature review differed from the laboratory-based studies more traditionally used to determine safety of new animal drugs (ie, evaluation of clinical and pathological changes in 4 groups of healthy laboratory dogs, with each group receiving either 0, 1, 3, or 5 times the therapeutic dose).[118] Although data were available from several studies[28,30,32,33] on bromide overdose, results in other publications provided summary information rather than the detailed individual data that are generally submitted for new animal drug approval. Much of the available literature was from client-owned pets with idiopathic epilepsy that were treated with KBr or PB under conditions of clinical use. Although the amount of detail for each animal was more limited, these pet owner reports included adverse events that were subtle and occurred after longer periods of administration (eg, PU and PD or behavioral signs). These may not be as readily noted in a laboratory setting or in a short-term clinical trial involving a selected population. Furthermore, the present systematic review allowed the evaluation of > 50 years of literature on the use of KBr in dogs, providing a volume and variety of evidence that far exceeded the data traditionally available to determine the safety of new animal drugs. Related findings in laboratory animals and humans that supported the available information for dogs could also be integrated. If KBr becomes more frequently used as monotherapy, future analyses may allow more complete systematic reviews and meta-analyses as well as further information on the safety questions raised in the present review.

On the basis of known pharmacological properties of bromides and specific information in the 111 publications identified in the present study, safety concerns for KBr could be evaluated and summarized for multiple physiologic systems. Bromide toxicosis in dogs was most frequently associated with high serum bromide concentrations; however, unusually sensitive dogs may also develop signs of toxicosis. The importance of monitoring clinical signs for individual animals should be emphasized because clinical signs may be a more useful measure of successful treatment than serum bromide concentration. Considerations that may affect the safety of KBr in individual animals include kidney and adrenal function, the amount of chloride in the diet, and the administration of IV fluids. Most adverse effects appeared to be reversible, but specific estimates of

incidence and comparative frequency of ADEs would provide a more thorough safety profile of KBr.

Neurologic signs were the most common type of ADE identified in the present study. Signs included sedation, irritability, restlessness, depression, behavioral changes, ataxia, hind limb paresis, mydriasis, stupor, and coma. Adverse neurologic effects were reported to be reversible and alleviated within several days by decreasing the PB dose or within hours by IV administration of saline solution. Adverse GI effects such as vomiting, transient diarrhea, and bloody feces have been reported in dogs but do not appear to require cessation of KBr treatment for resolution. Polyphagia and anorexia have been commonly reported for dogs receiving PB or KBr. Eating patterns and weight should be monitored in dogs receiving KBr, particularly because polyphagia can lead to garbage ingestion and other complications. There was not enough evidence at this time to conclude that dogs receiving KBr were at higher risk of developing pancreatitis than were dogs receiving other treatments. Pancreatitis may be related to polyphagia and garbage ingestion as well as to KBr treatment. Use of KBr in reproductively active dogs is of concern owing to the variety of reproductive effects reported in other species.

Results of the present review suggested that potential effects of KBr on thyroid function do not appear to be clinically important in dogs; however, more research is needed. Dermatologic reactions are not of concern with clinical KBr use in dogs, and respiratory disease in dogs is unlikely, considering the large amount of literature available and the very small number of cases reported.

Practitioners should use this information on KBr safety to tailor dosing and monitoring regimens specifically to individual dogs. Potassium bromide is not an appropriate therapeutic choice for every dog, which magnifies the importance of a valid veterinarian-client-patient relationship when determining whether an individual dog is a candidate for KBr treatment. Communication of the spectrum of potential adverse effects to owners and encouragement of close home monitoring for ADEs, especially for dogs on concurrent medications and with concurrent diseases, are important safety measures. Ultimately, availability of an FDA-approved KBr product with appropriate labeling information would provide better assurance for veterinarians and their clients of the quality, safety, and effectiveness of this product for animal use.

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