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Tolerable Levels of Nonclinical Vehicles and Formulations Used in Studies by Multiple Routes in Multiple Species With Notes on Methods to Improve Utility

Shayne Cox Gad[1], Charles B. Spainhour[2], Catherine Shoemake[3], Danielle R. Stackhouse Pallman[2], Alain Stricker-Krongrad[3], Philip A. Downing[4], Richard E. Seals[4], Leslie Anne Eagle[1], Kara Polhamus[5], and Jennifer Daly[5]

Abstract

Formulation of nonclinical evaluations is a challenge, with the fundamental need to achieve multiples of the clinical exposure complicated by differences in species and routes of administration-specific tolerances, depending on concentrations, volumes, dosing regimen, duration of each administration, and study duration. Current practice to approach these differences is based on individual experience and scattered literature with no comprehensive data source (the most notable exception being our 2006 publication on this same subject). Lack of formulation tolerance data results in excessive animal use, unplanned delays in the evaluation and development of drugs, and vehicle-dependent results. A consulting firm, a chemical company, and 4 contract research organizations conducted a rigorous data mining operation of vehicle data from studies dating from 1991 to 2015, enhancing the data from this author's 2006 publication (3 of the six 2015 contributors were also 2006 contributors). Additional data were found in the published literature. The results identified 108 single-component vehicles (and 305 combination formulations) used in more than 1,040 studies across multiple species (dog, primate, rat, mouse, rabbit, guinea pig, minipig, pig, chick embryo, and cat) by multiple routes for a wide range of study durations. The tabulated data include maximum tolerated use levels by species, route, duration of study, dose-limiting toxicity where reported, review of the available literature on each vehicle, guidance on syringe selection, volume and pH limits by route with basic guidance on nonclinical formulation development, and guidance on factors to be considered in nonclinical route selection.

Keywords

animals, nonclinical studies, routes, safety, species, vehicles, formulation, excipients

Introduction

From the point of initiation of development of a new drug or other test material, continuing on until the therapeutic enters serious clinical trials, perhaps the weakest link in investigations of both pharmacodynamic and toxicodynamic evaluations are formulations. In evaluating the nonclinical safety of potential new drugs, it is required that the material of interest be formulated in a manner that allows adequate administration of the test substance, with little or no effects on test animals attributable to the vehicles used in the delivery of the actual test material. The formulation must be chemically and physically suitable for the intended route of administration, optimize the stability of the active ingredient, and preferably (in most cases) maximize the systemic bioavailability of the drug. Because historically the process of vehicle selection has been mostly one of custom or personal choice, a range of vehicles have been most commonly used in formulation. Regrettably, information as to their suitability, utility, and the volume of nonclinical use limitations and species-specific considerations are not generally reflected in the literature or taught in any formal manner. Although recent years have seen the appearance of training courses on preformulation and articles on the development of early formulations (ie, Li and

[1] Gad Consulting Services, Raleigh, NC, USA
[2] Calvert Laboratories, Scott Township, PA, USA
[3] Sinclair Laboratories, Columbia, MO, USA
[4] BASi Laboratories, Mount Vernon, IN, USA
[5] MPI Laboratories, Mattawan, MI, USA

Corresponding Author:
Shayne Cox Gad, Gad Consulting Services, 4008 Barrett Drive Suite 201, Raleigh, NC 27609, USA.
Email: scgad@ix.netcom.com

Zhao[1]) proliferate, these concentrate on physical–chemical features. Certainly, such information on vehicle suitability for use in animals is not attainable in any organized source or on the Internet. This article, an expanded and updated version of the earlier work by Gad et al,[2] was undertaken to rectify the deficiency in information for those seeking to select suitable vehicles for nonclinical dosing of animals.

General Preclinical Formulation Principles

Dosing formulations for preclinical studies should be selected with consideration of a number of desirable characteristics.[3-6] A compilation of practical route-specific considerations to be taken into account when choosing vehicles and implementing their use in different species is presented in Table 1. Dose–volume limits provided by animal use and care guidances are presented in Table 2.[3,4] In Table 3, information on the selection of appropriate needles for use for different routes in different species is presented. In Table 4, an index of vehicles/excipients covered in this publication, their synonyms, basic characteristics, and the species and routes in which the vehicles were evaluated is provided. Tables 5 to 113 present data on acceptable vehicle usage by individual vehicles, whereas tabular data as to tolerated mixture formulations have been added to this article in the final table (Table 114).

Fundamental physicochemical considerations in the development of formulations should be observed. Preparation of the formulation should not involve heating of the test material to a point that alters its chemical or physical characteristics or so as to harm test animals receiving the formulation. If the material is a solid and is to be assessed for dermal effects and/or absorption, its shape and particle size should be preserved. Multicomponent test materials (mixtures) should be formulated so that the administered form accurately represents the original mixture (ie, components should not be selectively suspended or taken into solution). Formulations should preserve the chemical stability and identity of the test material. The formulation should minimize the total required test volumes and should consider effects on systemic pH and osmolarity. Formulations should use just enough solvent or vehicle to achieve the intended goal, unless there is reason to further dilute the active ingredient. The formulation should be as easy as possible to accurately administer. Highly viscous solutions or suspensions should be avoided in parenteral and intratracheal administrations.

A particular concern is oily solutions in rabbits—rabbits are particularly susceptible to respiratory infections, and withdrawal of a gavage tube after oral dosing leaves a film along the esophagus which can be aspirated into the lungs. The pH of dosing formulations should be between 5 and 9, if possible (although volume influences the limits of this range). Acids or bases should not be used to dilute or solubilize the test material (for both humane reasons and to avoid pH partitioning or stability issues in either the gut or the renal tubule). If a parenteral route is to be used, final solutions should be as nearly isotonic as possible, and if low or high pH solutions are used, injection volume should be minimized (it is possible to overwhelm a body's ability to maintain a stable systemic pH). Do not assume a solution will remain in solution upon injection into the bloodstream. It is usually a good idea to verify that the drug stays in solution upon injection by placing some drops into the plasma. Formulations for use by parenteral routes should be as endotoxin free as possible and sterile if for other than a few administrations. Particularly, if the test material (or formulation component) is biologically derived or produced, it should be evaluated for acceptable endotoxin content before actual formulation preparation to preclude problems. If use is to be more than a single injection, steps (such as 0.2 μm filtration) should be taken to ensure suitable sterility.[3,4]

Methods

Six separate organizations (BASi, Calvert, Gad Consulting Services [GCS], MPI, Exxon, and Sinclair Labs) undertook a review of their files to identify and collect data on control vehicles they had used in studies over approximately 25 years (1991-2015). Each in vivo study considered was conducted under good laboratory practices and were general toxicity studies with end points evaluated per International Conference on Harmonisation (ICH) or Organization for Economic Cooperation and Development (OECD) guidances. Every such study conducted during this period had its vehicle control group evaluated. If the vehicle was other than water, the highest no observable adverse effect level for the vehicle formulation used was determined and this was added to the database (note that this is different from merely providing literature values of lowest toxic dose levels). Extracted in this manner by the participating organizations, the maximum nontoxic volume is reported by species, route, and duration. The nature of any dose-limiting toxicity for a vehicle or vehicle combination was also identified. These data build on data published from the previous collection (Gad et al[2]), which had also included the former CIT Laboratories. In addition, this effort was supplemented by capturing some published literature. The total number of vehicles disclosed was large, with more than 108 different entities being reported.

The data were then assembled, quality assured, and organized in the tables presented, with materials listed in alphabetic order. These data tables are indexed in Table 4, which also provides basic physical–chemical data, synonyms, Chemical Abstracts Service (CAS) number, and general toxicity references on these vehicles.

The actual acceptable vehicle usage data are presented in Tables 5 to 113 with a single vehicle per table and arranged in alphabetical order by common name. New to this effort are the vehicle formulation combinations. A final table (Table 114) presents data on combination formulations that have been found useful and for which tolerable levels were reported. Most of these combination formulations are from contributed data—both from the initial collection (as yet unpublished) and from the more recently contributed data.

In Tables 5 to 114, for data sources, "Gad et al[2]" refers to single-vehicle data published in 2006, "Contributed data, 2006" refers to as yet unpublished contributed data from the

Table 1. Route-Specific Considerations.[2]

Route	Points of consideration	Possible adjustments to regimen to improve tolerance	References
Oral (PO)	(1) Stomach of some species (dog, rabbit) easily irritated (2) Stomach presents acid environment which may compromise the stability of active drug (3) Most absorption actually occurs in the intestines (4) Species-specific volume considerations	(1) Split dose over course of day (2) Use of capsules in dogs and minipigs to limit stomach irritation/emesis and to avoid acid stability of drug issues (3) Dose with food to improve absorption and tolerance in stomach (4) Intubation an option	Strickley[7,8]
Intra-articular (IA) injection into knee joints	(1) Species-specific volume considerations (2) Administration in pigs is limited as they only have such joints in their front limbs		
Intravenous (IV)	(1) Care must be taken to confirm that drug will stay in solution in the bloodstream (2) Need to ensure sterility of formulation (3) Vascular irritation, thrombosis, and hemolysis are concerns. Need to perform hemolysis and flocculation studies in advance (4) Species-specific volume considerations	(1) Infusion better tolerated than bolus (2) Decrease rate of infusion to decrease systemic/local C_{max} of drug (3) Need to ensure sterility of formulation (4) Vascular damage distal to site of injection is now a field of significant concern. May not always be due to IV administered drug (5) For repeated injections need to move site around	Lee et al[9]
Intramuscular (IM)	(1) Injection site irritation and infection is a concern (2) Species-specific volume considerations	(1) Adjust injection volume to multiple sites (2) For repeated injections need to move site around	
Intraperitoneal (IP)	(1) Scarring and inflammation responses at injection sites (2) Species-specific volume considerations (3) Need to make sure injection is into the peritoneal space		
Subcutaneous (SC)	(1) Nonpolar organic vehicles "defat" tissues if injected (2) Species-specific volume considerations	(1) Nonpolar organic vehicles all defat tissues if injected (2) May need to do multiple sites (3) Adjust volume	
Dermal (topical)	(1) Irritation and sensitization (2) Selection of correct model species essential to be relevant to humans (3) Need to consider formulation viscosity and changes with temperature (4) Need to consider solvents used in formulation, as choices can affect mechanism of absorption	(1) May need to wrap (2) May need to do multiple sites (3) May need to collar animals	Zesch[10]
Periocular	(1) Ocular irritation—tissue very sensitive to acid and base (2) Intraocular avoids local immune responses (3) Always keep in mind that anything injected in and around the eye is not going away quickly, so one is stuck with side effects. Be very concerned with pharmacology and half-life before injection (4) Length of needle for intraocular injection changes with species (5) Angle of injection changes with species		Ubels et al[11]
Inhalation	(1) Delivery mode/particle size dictate wherein respiratory tree delivery of drug occurs (2) Consider insufflation as alternative		Warheit et al[12]

Table 2. Volume Guidelines for Administration of Compounds by Route of Administration to Laboratory Animals.[3]

	Route																				
	Intranasal, µL/nostril	Gavage, mL/kg[a]		IV bolus,[b] mL/kg[a]		IP,[c] mL/kg[a]		SC,[d] mL/kg[a]		IM, mL/kg[a]		ID, mL/site[a]		IV infusion,[b] mL/kg		Continuous infusion		Intravaginal, mL	Intravitreal, µL/eye	Intra-articular, mL/joint		Perivenous/ periarterial, mL/ear
Species	Volume	Ideal	Maximum	Ideal	Maximum	Ideal	Maximum	Ideal	Maximum	Ideal	Maximum	Ideal	Maximum	Volume	Rate, mL/min	Maximum,[e] mL/kg/h	Catheter maintenance rate, mL/h	Maximum	Volume	Joint	Volume	Maximum
Mouse	25	10	40[f]	5	25	5-10	50	1-5	20[g]	0.1	1[h,i]	0.1	0.1	50	1	NIA		NIA	2	NIA	NIA	NIA
Rat	50	10	20[j]	1	20	5-10	20	1	20[g]	0.1	10[k]	0.1	0.1	50	1	5	0.1-0.5	0.35	5	Stifle Tarsal	0.1 0.05	NIA
Guinea pig	100	10	30	1	5	1-5	20	1-5	10[g]	0.1	0.5-1	0.1	0.1	10	1	NIA	NIA	NIA	NIA	NIA	NIA	NIA
Rabbit	200	1	20[l]	1[m]	10[m]	3	5[n]	1-2.5	10[g]	0.1-0.5	1	0.1	0.1	20	1	NIA	NIA	2.0	100	Stifle	0.5	0.5
Dog	500	5	20	1	10	3	5	0.5	2[g]	0.1-0.25	1[p,q]	0.1	0.1	20	5	5	1-2	2.0	100	Stifle	1	NIA
Nonhuman primate	200	5	10	1	10	3	5	0.5	2[g]	0.1-0.5	1[p,q]	0.1	0.1	20	1	5	1-2	NIA	50	NIA	NIA	NIA
Miniswine	NIA	NIA	NIA	1	10	1	5	1	3[g]	0.25	0.5[r]	0.1	0.1	10	1	5	1-2	NIA	NIA	NIA	NIA	NIA

Abbreviations: ID, Intradermal; IM, intramuscular; IP, intraperitoneal; IV, intravenous; NIA, no information available; SC, subcutaneous.

[a]Single dose per day except where noted otherwise.

[b]Solution properties such as tonicity, pH, and so on, need to be taken into account when approaching the volume limits or determining the volume to be infused IV. The recommended working range for pH is 4.5 to 8.0. The order of degree of tolerance of pH for different dosing routes is oral > intravenous > intramuscular > subcutaneous > intraperitoneal. Animal health must also be taken into consideration, such as kidney function and cardiovascular function. These systems must be normal to handle increased fluid volumes.

[c]When administering a solution IP, the viscosity, concentration, tonicity, and pH of the solution need to be taken into account.

[d]When administering a solution SC, the concentration, tonicity, and pH of the solution must be taken into account.

[e]Solution properties such as tonicity, pH, and so on, need to be taken into account when determining the volume that may be infused IV. Animal health must also be taken into consideration, such as kidney function and cardiovascular function. These systems need to be normal to handle increased fluid volumes.

[f]To accommodate a larger volume, the dose may be divided over time (eg, 20 mL/kg administered 4 times per day to reach a total of 80 mL/kg in a 24-hour period).

[g]If volumes greater than those cited previously are used, the volume must be divided over multiple sites.

[h]May be used if divided over multiple sites and alternating legs, maximum of 5 sites per leg. Final volume not to exceed 0.10 mL.

[i]0.05 mL total volume limit per site.

[j]To accommodate a larger volume, the dose may be divided over time (eg, 10 mL/kg administered 4 times per day to reach a total of 40 mL/kg in a 24-hour period).

[k]Up to 20 mL/kg if divided over multiple sites.

[l]Rabbits should not be fed prior to administration. Rabbits should be fed after the completion of dose administration.

[m]These volumes may also be used for intra-arterial injection.

[n]Not often used.

[o]Repeat dose 67 µL in the rabbit.

[p]3 mL total volume limit per site.

[q]3 mL total volume limit.

[r]5 mL total volume limit per site.

Table 3. Gavage Needle/Tube Size Recommendations.[3]

Species	
Mouse	The most commonly used gavage needle is a stainless steel curved 18-gauge needle with a 2.25-mm ball, but any other gauge needle that facilitates dose administration is acceptable
Rat	The most commonly used gavage needle is a stainless steel curved 16-gauge needle with a 3-mm ball, but any other gauge needle that facilitates dose administration is acceptable
Guinea Pig	The most commonly used gavage needle is a stainless steel curved 16-gauge needle with a 3-mm ball, but any other gauge needle that facilitates dose administration is acceptable
Rabbit	Either a flexible feeding tube or a stainless steel gavage needle may be used for oral gavage
	A 10F or 12F flexible feeding tube is most commonly used for larger rabbits and an 8F feeding tube is recommended for smaller rabbits, but any other size flexible feeding tube that facilitates dose administration may be used
	The most commonly used stainless steel gavage needle is a curved 12-gauge needle that is 6 in in length with a 3.5-mm ball, but any other gauge needle that facilitates dose administration is acceptable
Dog	A 30F, 30-in long, rubber tube is most commonly used, but any other size feeding tube that facilitates dose administration may be used
Nonhuman primate	A pediatric feeding tube (8F-12F) is most commonly used
Gottingen miniswine	An 18F, 16-in long, rubber tube is most commonly used, but any other size feeding tube that facilitates dose administration may be used
	Additional required equipment: dosing bench and bite bar

initial (2006) collection effort, and finally "New contributed data" refers to the more recent collection effort.

Formulation of drugs and, in a less sophisticated manner, all test materials for evaluation in intact animal systems (whether done for efficacy/pharmacology testing or for toxicology) is a field of expertise of its own. Although there are a few books on the formulation of human drugs (Racz[350], for example), no such volume is known to the authors to exist for data on tolerable levels of preclinical vehicles and formulations.

Although the development of pharmaceutical formulations for marketed clinical products is done in a rigorous manner, what is used for nonclinical testing (and early clinical formulation) is much more pragmatic. The reader is referred to Racz,[350] Yalkowsky,[351] and Weiner and Kotkoskie[352] for more detail as to the principles of vehicle and formulation component selection.

Recognizing that there were both general rules for selection of routes of administration in nonclinical sections as well as approaches to modify the administration by these routes, the first 2 authors have considered and added guidance on these points based on their combined 70 years' experience in the field (see Tables 1-3).

Discussion

Although some of the vehicle options and choices presented here may seem unusual, it should be noted that they represent actual uses ranging from the discovery phase of drug development through early nonclinical safety assessment, and in many cases, all the way through to use in marketed products. The reader is invited to inspect the Food and Drug Administration's (FDA) Inactive Ingredient List (IIG) at www.fda.gov/cder/drug/iig/inact.pdf for an idea of formulation components (excipients) used in clinical formulations.[353]

For all formulations, the ability to accurately administer an aliquot of what has been prepared, with each aliquot being of uniform content, is a primary requirement. With few exceptions (ie, capsule fills), this means achieving a solution or (second choice) stable suspension or emulsion.

Although the first choice for any systemic route is always a modification of an aqueous-based vehicle, the physiochemical characteristics of the test material dictate which available options are suitable,[350,351] especially in recent years where proteins and "rocks, gums, and tars" have become more common as potential drugs with high target receptor specificity but very poor physicochemical characteristics. One starts with either a polar or nonpolar solvent, depending on which one achieves adequate dissolution of the test material and works from there (usually by trying a combination of the two with the addition of a surfactant). Solubility enhancers such as the various cyclodextrins are also increasingly used, most commonly as accompanying primary components (with the drug moiety) along with an aqueous or other polar vehicle or solvent.

Recently, research has expanded the range of routes of use of some solvents such as Transcutol (Lyon, France). Because it is not just which chemical molecule(s) is administered but also at what concentration, by what route, and at what rate, Tables 1 to 3 were derived to present considerations and potential uses of these technique factors. A means of synthesis of considerations of tolerance, improvement in target site delivery, and bioavailability and considerations of formulation stability is badly needed and being explored.

To make the database presented here as accessible as possible and to broaden its content, GCS will again setup an online version with free access (see www.gadconsulting.com), which provides an online mechanism to submit new data and will maintain and update the electronic site for 5 years after publication of this article (until 2020). This portion of the Web site will be updated.

Table 4. Index of Vehicles and Excipients—Codex and Details.

Excipient/vehicle	Data in table # (T#); combination: # (C#)	CAS#	Synonyms	Formula	Key toxicity review articles/sources	Animal species evaluated	Administration routes evaluated
Acacia	T5, T114; C: 1-7	9000-01-5	*Acaciae gummi*	Natural product	Anderson[13]; Bachmann et al[14]; TOXNET[15]	Nonhuman primate, rat	PO
Acetate buffer	T114; C: 8, 9, 119, 138-141	71-50-1	Acetate ion	C_2-H_3-O_2	TOXNET[16]	Nonhuman primate, minipig, mouse, rat	IM, IV, PO
Acetic acid	T6, T114; C: 10, 12	64-19-7	Ethanoic acid	$C_2H_4O_2$	Schonwald[17]; Szilagyi[18]; TOXNET[19]	Dog, mouse, rat	IV, PO
Acetone	T7, T114; C: 11	67-64-1	2-Propanone	C_3-H_6-O	TOXNET[20]	Guinea pig, mouse, rabbit, rat	Dermal, PO
Acetonitrile	T114; C: 12	75-05-8		C_2-H_3-N	TOXNET[21]	Dog	PO
Acetylated lanolin alcohol	T114; C: 174	61788-49-6		N/A	TOXNET[22]	Minipig	Topical
Acetylmethylamide	T8; -	79-16-3	N-Methylacetamide	C_3H_7NO	TOXNET[23]	Nonhuman primate	PO
Alcohol denatured SDA	T114; C: 234					Minipig	Topical
Alginic acid	T9; -	9005-32-7	Norgine		JECFA[24]; TOXNET[25]	Rat	IP
Anecortave acetate	T10; -	7753-60-8		$C_{23}H_{30}OS$	Jockovich et al[26]; Talsma[27]; TOXNET[28]	Rat	SC
Antifoam 1510-US	T114; C: 1, 100, 101		Silicone emulsion		Dow Corning[29]	Rat	PO
Avicel CL-611	T11; -		Microcrystalline cellulose and carboxymethylcellulose sodium, NF, EP		TOXNET[30]	Dog	PO
Balanced salt saline	T12; -					Rabbit	Intravitreal
Basal salt solution	T13; -					Mouse	Subretinal injection
Benzoic acid	T14; -	65-85-0	Benzoic acid	$C_7H_6O_2$	David et al[31]; Nair[32]; TOXNET[33]	Rat	PO
Benzyl alcohol	T114; C: 8, 9, 13, 14, 31	100-51-6		C_7-H_8-O	Nair[32]; TOXNET[34]	Cat, dog, nonhuman primate, rat	IV, PO, topical
β-Cyclodextrin	T15; -	7585-39-9	β-Dextrin; betadex	$C_{42}H_{70}O_{35}$	Albers and Muller[35]; Challa et al[36]; Marttin et al[37]; Rajewski et al[38]; TOXNET[39]; Toyoda et al[40]; Waner et al[41]	Dog, mouse, nonhuman primate, rat	IP, IV, PO
BHA	T114; C: 73	25013-16-5	Butylated hydroxyanisole	C_{11}-H_{16}-O_2	TOXNET[42]	Minipig	Topical
BHT	T114; C: 73, 127, 164, 165	128-37-0	Butylated hydroxytoluene	$C1_5H_{24}O$	Briggs et al[43]; Lanigan and Yamarik[44]; Nakagawa et al[45]; TOXNET[46]	Cat, dog, minipig, mouse, rat	IV, PO, topical
Bicarbonate buffer	T16; -	71-52-3	Bicarbonate ion	C-H-O_3	TOXNET[47]	Mouse	PO
Calcium chloride	T17; -	10035-04-8		Ca-Cl_2.$2H_2$-O	TOXNET[48]	Mouse	IV, SC
Canola oil	T18; -	120962-03-0	Canbra oil	Natural product	Evangelista et al[49]; TOXNET[50]	Dog	PO
Capmul MCM	T114; C: 15	26402-22-2, 26402-26-6	Medium-chain mono- and diglycerides	N/A	Susananta et al[51]	Nonhuman primate	PO
Capmul MCM NF	T114; C: 16, 255	91744-32-0, 26402-22-2, 26402-26-6	Glyceryl caprylate/caprate	N/A		Dog, rat	PO
Capmul PG 8	T114; C: 242, 243					Dog, rat	PO
Capryol 90	T19; -	31565-12-5	Propylene glycol monocaprylate (type II) NF; Capmul PG-8	$C_{11}H_{22}O_3$	Li et al[52]; Cho and Gwak[53]	Dog, rabbit, rat	Dermal, ocular, PO
Captisol	T20, T114; C: 17, 191	182410-00-0	β-Cyclodextrin sulfobutyl ether, sodium salt (CDSBE)	$C_{42}H_{70}$-nO_{35}*$(C_4H_8SO_3Na)n$	Albers and Muller[35]; Challa et al[36]; Marttin et al[37]; TOXNET[54]	Dog, mouse, nonhuman primate, rat	IV, PO, SC

(continued)

Table 4 (continued)

Excipient/vehicle	Data in table # (T#); combination: # (C#)	CAS#	Synonyms	Formula	Key toxicity review articles/sources	Animal species evaluated	Administration routes evaluated
Carbomer 974P	T114; C: 234, 235, 272	151687-96-6	Carbomer homopolymer type B (allyl pentaerythritol cross-linked)	N/A	TOXNET[55]	Minipig, mouse	Topical
Carbopol Ultrez 10	T114; C: 61	195739-91-4		N/A	TOXNET[56]	Minipig	Topical
Carboxymethylcellulose	T21, T114; C: 20-30, 301	9000-11-7	CMC; acetic acid; 2,3,4,5,6-pentahydroxyhexanal	N/A	Gupta et al[57]; Mehlman[58]; TOXNET[59]	Dog, minipig, mouse, nonhuman primate, rabbit, rat	IA, PO, SC
Carboxymethylcellulose calcium	T22; -	9050_04_8	Calcium CMC; carmellose calcium	N/A	TOXNET[60]	Dog	PO
Carboxymethylcellulose sodium	T23, T114; C: 269, 270	9004-32-4	Sodium CMC; carmellose sodium	N/A	Bachmann et al[14]; Bar et al[61]; Cavender[62]; Freeman et al[63]; TOXNET[64]	Mouse, rabbit, rat	PO
Cavisol	T114; C: 185, 186					Dog, rat	PO
Cetostearyl alcohol	T114; C: 288	67762-27-0		N/A	TOXNET[65]	Minipig	Topical
Cetyl acetate	T114; C: 174	629-70-9		C_{18}-H_{36}-O_2	TOXNET[66]	Minipig	Topical
Cetyl alcohol	T24, T114; C: 163	36653-82-4	Hexadecan-1-ol; 1-hexadecanol	$C_{16}H_{34}O_1$	Bevan[67]; TOXNET[68]	Minipig, mouse	IP, topical
Citrate buffer	T25, T114; C: 18, 19, 126, 147, 229	77-92-9	Sodium citrate–citric acid buffer	C_6-H_8-O_7	Schonwald[69]	Dog, nonhuman primate, rat	IV, PO, SC
Citric acid buffer	T26, T114; C: 13, 38, 58, 95, 302	77-92-9		C_6H_{807}*H_{20}	Szilagyi[70]	Cat, mouse, nonhuman primate, rat	PO, topical
Coconut oil	T114; C: 288	8001-31-8		Natural product	National Toxicology Program[71]; Shadnia et al[72]; TOXNET[73]	Minipig	Topical
Collagen matrix	T27; -	9007-34-5	Collagen human	Natural product	McCarthy et al[74]; Clark et al[75]	Nonhuman primate, rabbit	Implantation in humerus bone,
Corn oil	T28, T114; C: 31-33	8001-30-7	Corn germ oil, glyceridic	Natural product	DeWitt et al[76]; Dupont et al[77]; TOXNET[78]; Wu et al[79]	Chicken embryo, dog, mouse, nonhuman primate, rabbit, rat	Implantation injection into egg, PO
Cottonseed oil	T29; -	8001-29-4		Natural product	TOXNET[80]	Dog	SC
Cyclodextrin	T114; C: 34-37	12619-70-4			TOXNET[81]	Rat	PO
Cyclohexane	T30, T114; C: 11	110-82-7	Hexahydrobenzene; hexamethylene; hexanaphthene	C_6H_{12}	Gad[82]; Kreckmann et al[83]; Malley et al[84]; TOXNET[85]	Rabbit, rat	PO, dermal
Cyclomethicone NF	T114; C: 174, 288	69430-24-6		N/A	TOXNET[86]	Minipig	Topical
DAM	T114; C: 179-182	57-71-6	Diacetylmonoxime; 2,3-butanedione 2-oxime	C_4-H_7-N-O_2	TOXNET[87]	Dog, rat	IV
Dextrose	T31, T114; C: 17, 39, 40, 108-111, 184, 277	50-99-7	Glucose; D-glucose, anhydrous; dextrosol	$C_6H_{12}O_6$	Buard et al[88]; Robertson et al[89]; TOXNET[90]	Cat, dog, minipig, nonhuman primate, rabbit, rat	IV, IV/PO, perivascular, PO, SC
Dichlorvos	T32; -	62-73-7	DDVP; dichlorophos; dichlorphos; divipan; 2,2-dichloroethenyl dimethyl phosphate	$C_4H_7Cl_2O_4P$	TOXNET[91]	Nonhuman primate	IV
Diethylacetamide	T33, T114; C: 41	685-91-6	N,N-Diethylacetamide	C_6-H_{13}-N-O	Budden et al[92]; Caujolle et al[93]; ChemIDPlus[94]; TOXNET[95]	Cat, chicken, dog, mouse, rabbit, rat	IP, IV
Diethyleneglycol monoethylether	T34; -	111-90-0	2-(2-Ethoxyethoxy)ethanol; DEGEE; carbitol	C_6-H_{14}-O_3	Hardin[96]; Hardin et al[97]; TOXNET[98]	Nonhuman primate	IV

(continued)

Table 4 (continued)

Excipient/vehicle	Data in table # (T#); combination: # (C#)	CAS#	Synonyms	Formula	Key toxicity review articles/sources	Animal species evaluated	Administration routes evaluated
Dimethicone	T114; C: 301	9006-65-9		N/A	TOXNET[99]	Rabbit	PO
Dimethiconol Blend 20	T114; C: 38	70131-67-8 and 63148-62-9	Dimethicone and dimethiconol		Dow Corning[100]	Minipig	Topical
Dimethyl acetamide	T35, T114; C: 187-188	127-19-5	DMA; N,N-dimethylacetamide; acetdimethylamide	C_4-H_9-N-O	TOXNET[101]	Chicken, dog, mouse, rabbit, rat	Dermal, inhalation, IP, IV, PO
Dimethylsulfoxide	T36, T114; C: 2-5, 43-57, 91, 94, 157, 158, 193-197	67-68-5	DMSO	C_2H_6OS	Ali[102]; Augustine et al[103]; Bartsch et al[104]; Pestel et al[105]; PharmPK[106]; RTECS[107]; Ruble et al[108]; Schonwald[17]; Sodicoff et al[109]; TOXNET[110]; White et al[111]; Wood et al[112]	Dog, guinea pig, minipig, mouse, non-human primate, rabbit, rat	IP, IV, PO, SC
Disodium hydrogen phosphate dihydrate	T114; C: 42	10140-65-5	Sodium phosphate, dibasic	H_3-O_4-P.x-H_2-O.2Na	TOXNET[113]	Nonhuman primate	SC
Docosanol	T114; C: 288	661-19-8	1-Docosanol	C_{22}-H_{46}-O	TOXNET[114]	Minipig	Topical
Dulbecco modified PBS	T37; -		Dulbecco modified phosphate-buffered saline solution			Rat	IV (tail vein)
Dulbecco PBS	T38; -		Dulbecco phosphate-buffered saline solution			Rat	PO
EDTA	T114; C: 58-61	60-00-4	Ethylenediaminetetraacetic acid; edetic acid	C_{10}-H_{16}-N_2-O_8	Cavender[115]; Heimbach et al[116]; Lanigan and Yamarik[117]; TOXNET[118]	Minipig, nonhuman primate, rat	Dermal, IV, topical
Ethanol	T39, T114; C: 32, 33, 38, 40, 61-73, 98, 99, 108-111, 124, 148-156, 160, 161, 164, 165, 175, 184, 191, 196-205, 211, 212, 223, 224, 239-250, 253, 254, 259, 260, 283, 285, 286, 290	64-17/5	Ethyl alcohol	C_2H_6O	Bartsch et al[104]; Bevan[119]; Church and Witting[120]; Fort et al[121]; Moorman et al[122]; Rowe et al[123]; Ruble et al[108]; Sivilotti[124]; TOXNET[125]	Dog, guinea pig, minipig, mouse, nonhuman primate, rat	Dermal, IP, IV, PO, SC, topical
Fumaric acid	T114; C: 90	110-17-8	2-Butenedioic acid	C_4-H_4-O_4	TOXNET[126]	Dog	PO
Gelatin	T40, T114; C: 74, 120	9000-70-8			TOXNET[127]	Dog, nonhuman primate	PO
Gelatin phosphate buffer	T41; -					Minipig	Topical
Gelucire	T114; C: 75					Minipig	PO
Gelucire 44/14	T42, T114; C: 76, 77	121548-04-7	PEG-32 glyceryl laurate		Cavender[128]; Dordunoos et al[129]; Kawakami et al[130]; Ratsimbazafy et al[131]; TOXNET[132]; Working et al[133]	Dog, minipig, mouse rabbit, rat	Dermal, ocular, PO
Gelucire 50/13	T43; -	121548-05-8	G-50-13		Fini et al[134]; Passerini et al[135]; Ratsimbazafy et al[131]; Sharma[136]; TOXNET[137]	Rat	PO
Gluconic acid	T44; -	133-42-6		C_6-H_{12}-O_7	TOXNET[138]	Dog, rat	PO
Glycerol	T45, T114; C: 61, 90, 239, 240	56-81-5	Glycerine; glycerin	$C_3H_8O_3$	Anderson et al[139]; Bartsch et al[104]; Cosmetic Ingredient Review[140]; TOXNET[141]	Dog, guinea pig, minipig, mouse, non-human primate, rabbit, rat	IP, IV, PO, SC, topical
Glyceryl stearate SE	T114; C: 163	11099-07-3		C_{18}-H_{36}-O_2.x-C_3-H_8-O_3	Cosmetic Ingredient Review[140]	Minipig	Topical
Glycofurol	T46; -	31692-85-0		(C_2-H_4-O)mult-C_5-H_{10}-O_2	Ruble et al[108]; TOXNET[142]	Dog	IV

(continued)

Table 4 (continued)

Excipient/vehicle	Data in table # (T#); combination: # (C#)	CAS#	Synonyms	Formula	Key toxicity review articles/sources	Animal species evaluated	Administration routes evaluated
Glycol dimethacrylate cross polymer	T114; C: 127					Rat	Topical
Gum tragacanth	T47; -	9000-65-1		Natural product	Anderson DM[143]; Bachmann et al[14]; Hagiwara et al[144]; TOXNET[145]	Mouse	PO
Gum xanthan	T48, T114; C: 163, 305	11138-66-2	Keltrol	$(C_{35}H_{49}O_{29})_n$	TOXNET[146]	Minipig, rabbit, rat	PO, topical
Hexylene glycol	T114; C: 38	107-41-5		C_6-H_{14}-O_2		Minipig	Topical
Histidine	T114; C: 78-80, 287	71-00-1		C_6-H_9-N_3-O_2	TOXNET[147]	Dog, rat	IV, SC
Hydrochloric acid	T49; -	7647-01-0	Hydrogen chloride; muriatic acid; chlorohydric acid; chlorane	HCl	TOXNET[148]	Dog, rat	PO
Hydrogenated castor oil	T114; C: 288	8001-78-3			TOXNET[149]	Minipig	Topical
Hydroxyethylcellulose	T50, T114; C: 100, 101	9004-62-0	Natrosol; 2-hydroxyethyl ether cellulose		Pestel et al[105]; TOXNET[150]	Rat	PO
Hydroxypropyl β-cyclodextrin	T51, T114; C: 91-99	128446-35-5	2-hydroxypropyl β-cyclodextrin (HPβCD); hydroxypropyl betadex; Cavasol W7 HP	$C_{54}H_{102}O_{39}$	Albers and Muller[35]; Challa et al[36]; Coussement et al[151]; Gerloczy et al[152]; Gould and Scott[153]; Marttin et.al[37]; Pestel et al[105]; Ruble et al[108]; Stella and He[154]; Thackaberry et al[155]; TOXNET[156]	Dog, mouse, nonhuman primate, rabbit, rat	Intranasal, IP, IV, PO, SC
Hydroxypropyl cellulose	T52, T114; C: 38	9004-64-2	Hyprolose (INN), 2-hydroxypropyl cellulose	N/A	Cavender[157]; TOXNET[158]	Minipig, rat	PO, topical
Hydroxypropyl methylcellulose	T53, T114; C: 81-87, 90	9004-65-3	Benecel MHPC, hypromellose, HPMC; Methocel E50 Premium LV	N/A	Feitoza et al[159]; Geerling et al[160]; Maki et al[161]; Mehlman[162]; Obara et al[163]; Rosen et al[164]; Thackaberry et al[155];TOXNET[165]	Dog, minipig, mouse, nonhuman primate, rat	IP, PO
Hydroxypropyl methylcellulose acetate succinate	T114; C: 88, 89, 291-294	71138-97-1	Hypromellose acetate succinate; HPMC AS	N/A	TOXNET[166]	Dog, minipig, mouse, rabbit, rat	PO
Hymetellose	T114; C: 102	9032-42-2	Methyl hydroxyethylcellulose; Tylose MH50	N/A	TOXNET[167]	Rabbit	PO
Hypotonic PBS	T54; -					Dog, rat	IV
Imwitor 742	T114; C: 103-105		Caprylic/capric glycerides; glyceryl monocaprylocaprate, type I		Susananta et al[51]	Hamster, nonhuman primate, rat	PO
Isopropyl alcohol	T55, T114; C: 14	67-63-0	2-propanol; isopropanol; sec-propyl alcohol	C_3H_8O	Allen et al[168]; Bevan C[169]; Burleigh-Flayer H[170]; Church and Witting[120]; Sivilotti[124]; TOXNET[171]; Tyl et.al[172]	Dog, rabbit	Dermal, topical
Isopropyl myristate	T56, T114; C: 163, 234, 235	110-27-0	1-Methylethyl tetradecanoate; Crodamol IPM	$C_{17}H_{34}O_2$	Campbell and Bruce[173]; Komatsu et al[174]; TOXNET[175]	Minipig, mouse, rabbit	Dermal, topical
Isotonic saline	T114; C: 117					Rat	PO
Kolliphor	T114; C: 43, 48		Cremophor; Polyoxyl castor oil			Nonhuman primate	IV, PO
Kolliphor EL	T57, T114; C: 15, 16, 62, 63, 106, 108-111, 170-173, 209	61791-12-6	Cremophor EL; Polyoxyl castor oil; Polyoxyl 35 castor oil	N/A	Gelderblom et al[176]; Gupta et al[57]; Lorenz et al[177]; PharmPK[178]; Ramadan et al[179]; Stokes et al[180]; TOXNET[181]	Dog, mouse, nonhuman primate, rat	IV, PO

(continued)

Table 4 (continued)

Excipient/vehicle	Data in table # (T#); combination: # (C#)	CAS#	Synonyms	Formula	Key toxicity review articles/sources	Animal species evaluated	Administration routes evaluated
Kolliphor ELP	T58; -	61791-12-6	Cremophor EL; Polyoxyl castor oil; Polyoxyl 35 castor oil	N/A	TOXNET[181]	Dog	
Kolliphor HS 15 (see also: Solutol HS 15)	T114; C: 113					Minipig	PO
Kolliphor RH 40	T59, T114; C: 107, 207-209, 231	61788-85-0	Cremophor RH 40; PEG-40 hydrogenated castor oil; Polyoxyl 40 hydrogenated castor oil; macrogolglycerol hydroxystearate	N/A	Gupta et al[57]; Stokes et al[180]; TOXNET[182]	Dog, rat	IV, PO
Labrafil M1944	T60, T114; C: 112, 114	62563-68-2	Labrafil	N/A	Beckwith-Hall et al[183]; TOXNET[184]	Dog, rabbit, rat	Dermal, PO
Labrasol	T61, T114; C: 113-115, 209	85536-07-8	Polyglycolyzed glycerides	N/A	Hu et al[185]; Hu et al[186]	Dog, minipig, rabbit, rat	Dermal, IV, ocular, PO
Lactated Ringer	T114; C: 116	8026-79-7	Sodium chloride, sodium lactate, potassium chloride, and calcium chloride; compound sodium lactate injection	C_3-H_6-O_3.Ca-Cl_2.Cl-K.Na	TOXNET[187]	Nonhuman primate	IV
Lactic acid	T114; C: 296-298	50-21-5	2-Hydroxypropanoic acid	C_3-H_6-O_3	TOXNET[188]	Dog, rat	IA, IV
Lactose	T62, T114; C: 261-264, 278-281	63-42-3(anhydrous)	O-β-D-Galactopyranosyl-(1->4)-α-D-glucopyranose	$C_{12}H_{22}O_{11}$ (anhydrous)	Ahmad et al[189]; Baldrick and Bamford[190]; TOXNET[191]	Dog, nonhuman primate, rat	Inhalation, IV, SC
Lanolin	T63; -	8006-54-0	Wool wax	N/A	Kligman[192]; TOXNET[193]	Minipig, rabbit	Dermal, topical
Lanolin alcohol NF	T114; C: 174	8027-33-6	Eucerin	Natural product	TOXNET[194]	Minipig	Topical
L-Arginine HCl USP	T114; C: 163, 289	15595-35-4	L-Arginine hydrochloride	C_6-H_{14}-N_4-O_2.x-Cl-H	TOXNET[195]	Minipig, nonhuman primate	SC, topical
L-ascorbic acid	T114; C: 117	50-81-7	Cevatine, cevex, cevital	$C_6H_8O_6$	Bendich and Cohen[196]; Dykes and Meier[197]; Temple[198]; TOXNET[199]	Rat	PO
Lauroglycol 90	T64; -	27194-74-7	Propylene glycol monolaurate; lauric acid, monoester with propane-1,2-diol	C_{15}-H_{30}-O_3	Bartsch et al[104]; Liu H et al[200]; TOXNET[201]	Rabbit, rat	Dermal, ocular, PO
Maltitol solution	T65; -	9053-46-7	Liquid maltitol; Lycasin	$C_{12}H_{24}O_{11}$ + $C_6H_{14}O_6$	Modderman[202]; Walker and El Harith[203]; TOXNET[204]	Rat	IP
Maltol	T66; -	118-71-8	2-methyl pyromeconic acid; 2-methyl-3-hydroxy-4-pyrone	$C_6H_6O_3$	Hironishi et al[205]; Murakami et al[206]; TOXNET[207]	Guinea pig, rabbit	PO
Mannitol	T67, T114; C: 43, 48, 74, 118-123, 159, 233, 274, 275, 282	69-65-8	D-Mannitol	$C_6H_{14}O_6$	Horvath et al[208]; Lina et al[209]; TOXNET[210]	Dog, minipig, mouse, nonhuman primate, rabbit, rat	IM, IV, PO, SC
Methane sulfonic acid	T114; C: 124	75-75-2	Methylsulfonic acid	CH_4O_3S	Shertzer[211]; TOXNET[212]	Rat	PO
Methocel	T114; C: 125					Nonhuman primate; rat	PO
Methyl methacrylate	T114; C: 127	80-62-6		C_5-H_8-O_2	TOXNET[213]	Rat	Topical
Methylcellulose	T68, T114; C: 88, 89, 126, 129-146, 178, 183, 295	9004-67-5	Cellulose methyl ether; Methocel A4M Premium	N/A	Bachmann et al[14]; Gupta et al[58]; Mehlman[214]; Sellers et al[215]; TOXNET[216]	Dog, guinea pig, mouse, nonhuman primate, rabbit, rat	IV, PO, topical
Methylparaben	T114; C: 128, 147, 174	99-76-3	4-Hydroxybenzoic acid, methyl ester	C_8-H_8-O_3	TOXNET[217]	Minipig	SC, topical

(continued)

Table 4 (continued)

Excipient/vehicle	Data in table # (T#); combination: # (C#)	CAS#	Synonyms	Formula	Key toxicity review articles/sources	Animal species evaluated	Administration routes evaluated
Methylpyrrolidone	T69, T114; C: 75-77	872-50-4	N-methyl-2-pyrrolidone, 1-methyl-2-pyrrolidone, Pharmasolv, N-methyl-2-pyrrolidone (NMP)	C_5H_9NO	Bartsch et al[104]; Kennedy[218]; Lee KP et al[219]; Ruble et al[108]; Solomon et al[220]; TOXNET[221]	Dog, minipig, mouse	IV, PO
Mineral oil	T70, T114; C: 288	8012-95-1	Liquid paraffin	Natural product	Carlton et al[222]; Dalbey and Biles[223]; Nash et al[224]; TOXNET[225]; Trimmer et al[226]	Cat, dog, guinea pig, minipig, mouse, rat	PO, topical
Myristyl alcohol	T114; C: 288	112-72-1	1-Tetradecanol	C_{14}-H_{30}-O	TOXNET[227]	Minipig	Topical
Neobee 1053 oil	T114; C: 164, 165	73398-61-5	Medium-chain triglycerides	N/A	Bellantone[228]; Traul et al[229]; Susananta et al[51]; Wieland et al[230]	Mouse, rat	IV, PO
Octoxynol-40	T114; C: 167-169	9002-93-1		(C_2-H_4-O)mult-.C_{14}-H_{22}-O (C_2-H_4-O)mult-C_{14}-H_{22}-O C_{34}-H_{62}-O_{11}	TOXNET[231]	Dog, rabbit	Ocular
Oleic acid NF	T114; C: 163, 170-174	112-80-1	9-Octadecenoic acid	C_{18}-H_{34}-O_2	TOXNET[232]	Minipig	Topical
Oleyl alcohol NF	T114; C: 174	143-28-2		C_{18}-H_{36}-O	TOXNET[233]	Minipig	Topical
Olive oil	T71, T114; C: 174	8001-25-0		Natural product	Evangelista et al[49]; TOXNET[234]	Minipig, rat	PO, topical
Ora-Plus suspension	T114; C: 34-37		Purified water, microcrystalline cellulose, carboxymethylcellulose sodium, xanthan gum, carrageenan, calcium sulfate, trisodium phosphate, citric acid, and sodium phosphate as buffers, dimethicone antifoam emulsion. Preserved with methylparaben and potassium sorbate		Paddock[235]	Rat	PO
Panthenol	T114; C: 61	16485-10-2	Dexpanthenol	C_9-H_{19}-N-O_4	TOXNET[236]	Minipig	Topical
Peanut oil	T72, T114; C: 175	8002-03-7	Arachis oil; Fletcher	Natural product	Cosmetic Ingredient Review[237]; Patel et al[238]; TOXNET[239]	Dog, rat	PO, SC
Peceol	T114; C: 176, 177	25496-72-4	Glyceryl monooleate NF; monoolein	C_{21}-H_{40}-O_4	TOXNET[240]	Dog, rat	PO
PEG 200	T73, T114; C: 131, 183, 184	25322-68-3	Polyethylene glycol 200	(C_2-H_4-O)mult-H_2-O	Cavender[128]; Dordunoos et al[129]; Smyth et al[241]; Smyth et al[242]; Smyth et al[243]; Quadbeck[244]; TOXNET[245]; Working et al[133]	Minipig, nonhuman primate, rabbit, rat	IP, IV, PO
PEG 300	T74, T114; C: 106, 185-190, 290	25322-68-3	Polyethylene glycol 300	(C_2-H_4-O)mult-H_2-O	Carpenter and Shaffer[246]; Cavender[128]; Dordunoos et al[130]; Patel et al[238]; Rowe and Wolf[247]; Smyth et al[241]; Smyth et al[242]; Smyth et al[243]; TOXNET[245]; Working et al[133]	Cat, dog, guinea pig, mouse, rabbit, rat	IP, IV, PO, PO mucosa

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Table 4 (continued)

Excipient/vehicle	Data in table # (T#); combination: # (C#)	CAS#	Synonyms	Formula	Key toxicity review articles/sources	Animal species evaluated	Administration routes evaluated
PEG 400	T75, T114; C: 44-47, 50-52, 75-77, 107, 115, 151, 152, 170-173, 176, 177, 191-231, 254, 276	25322-68-3	Polyethylene glycol 400	$(C_2\text{-}H_4\text{-}O)mult\text{-}H_2\text{-}O$	Bartsch et al[104]; Cavender[128]; Dordunoos et al[129]; Fort et al[121]; Gupta et al[57]; Gutiérrez-Cabano[248]; Hermansky et al[249]; Li et al[250]; Patel et al[238]; Rowe and Wolf[247]; Ruble et al[108]; Shideman and Procita[251]; Smyth et al[241]; Smyth et al[242]; Smyth et al[243]; Stokes et al[180]; Strickley[8]; Thackaberry[252]; TOXNET[245]; Working et al[133]	Dog, guinea pig, minipig, mouse, nonhuman primate, minipig, rabbit rat	Dermal, IP, IV, PO, topical
PEG 600	T76; -	25322-68-3	Polyethylene glycol 600	$(C_2\text{-}H_4\text{-}O)mult\text{-}H_2\text{-}O$	Pfordte[253]; Rowe and Wolf[247]; Smyth et al[243]; TOXNET[245]	Rat	IP, IV, PO
PEG 810	T77; -	25322-68-3	Polyethylene glycol 810	$(C_2\text{-}H_4\text{-}O)mult\text{-}H_2\text{-}O$	Käber[254]; TOXNET[245]	Rat	IV, SC
PEG 1,000	T78; -	25322-68-3	Polyethylene glycol 1,000	$(C_2\text{-}H_4\text{-}O)mult\text{-}H_2\text{-}O$	Shideman and Procita[251]; Smyth et al[242]; TOXNET[245]	Mouse, rabbit, rat	IP, IV, PO
PEG 1,500	T79; -	25322-68-3	Polyethylene glycol 1,500	$(C_2\text{-}H_4\text{-}O)mult\text{-}H_2\text{-}O$	Rowe and Wolf[247]; Smyth et al[255]; Smyth et al[242]; Smyth et al[256]; Smyth et al[243]; TOXNET[245]	Rat	IP, IV, PO
PEG 1,540	T80; -	25322-68-3	Polyethylene glycol 1,540	$(C_2\text{-}H_4\text{-}O)mult\text{-}H_2\text{-}O$	Smyth et al[242]; Smyth et al[243]; TOXNET[245]	Dog, rabbit, rat	IP, IV, PO
PEG 4,000	T81, T114; C: 53, 54	25322-68-3	Polyethylene glycol 4,000	$(C_2\text{-}H_4\text{-}O)mult\text{-}H_2\text{-}O$	Rowe and Wolf[247]; Shideman and Procita[251]; Smyth et al[256]; Smyth et al[255]; Smyth et al[242]; Smyth et al[243]; TOXNET[245]	Dog, mouse, rabbit, rat	IP, IV, PO
PEG 6,000	T82; -	25322-68-3	Polyethylene glycol 6,000	$(C_2\text{-}H_4\text{-}O)mult\text{-}H_2\text{-}O$	Smyth et al[242]; Smyth et al[243]; TOXNET[245]	Rabbit, rat	IP, IV, PO
PEG 10,000	T83; -	25322-68-3	Polyethylene glycol 10,000	$(C_2\text{-}H_4\text{-}O)mult\text{-}H_2\text{-}O$	Smyth et al[242]; TOXNET[245]	Rat	IP, PO
PEG 400,000	T84; -	25322-68-3	Polyethylene glycol 400,000	$(C_2\text{-}H_4\text{-}O)mult\text{-}H_2\text{-}O$	Smyth et al[242]; Smyth et al[257]; TOXNET[245]	Rat	IV, PO
Petrolatum	T85; -	8009-03-8	Yellow soft paraffin; petroleum jelly	N/A	TOXNET[258]	Rabbit	Dermal
Phenoxyethanol	T114; C: 234, 235, 272	122-99-6	2-Phenoxyethanol	$C_8\text{-}H_{10}\text{-}O_2$	TOXNET[259]	Minipig, mouse	Topical
Phosal 53 MCT	T114; C: 231		Lecithin in caprylic/capric triglycerides, alcohol, glyceryl stearate, oleic acid, and ascorbyl palmitate		American Lecithin[260]; Susananta et al[51]	Rat	PO
Phosphate	T114; C: 59, 60, 232	14265-44-2	Phosphate ion	$O_4\text{-}P$	TOXNET[261]	Nonhuman Primate	IV
Phosphate buffer	T114; C: 233					Rat	SC
Phosphate-buffered saline	T86, T114; C: 28-30		Phosphate-buffered saline			Dog, minipig, mouse, nonhuman primate, rabbit, rat	IA, IV, PO, SC, topical
Polawax	T114; C: 234, 235		Emulsifying wax		Carlton et al[222]	Minipig, mouse	Topical
Poloxamer 124	T114; C: 225-228, 231					Dog, mouse, rat	PO

(continued)

Table 4 (continued)

Excipient/vehicle	Data in table # (T#); combination: # (C#)	CAS#	Synonyms	Formula	Key toxicity review articles/sources	Animal species evaluated	Administration routes evaluated
Poloxamer 188	T87, T114; C: 42, 83-85, 102, 236-238	9003-11-6	Poloxalene	$(C_3-H_6-O.C_2-H_4-O)x-$	Benita[262]; Curry et al[263]; Frim et al[264]; Grindel et al[265]; Lemieux et al[266]; Serbest et al[267]; TOXNET[268]	Dog, minipig, mouse, nonhuman primate, rabbit, rat	PO, SC
Polyethylene terephthalate	T114; C: 162		PET			Rat	IV
Poly(glycolide-co-dl-lactide) microspheres	T88; -	26780-50-7				Dog	Into periodontal pockets
Polyglyceryl oleate	T89; -	9007-48-1	1,2,3-Propanetriol, homopolymer, (Z)-9-octadecenoate; decaglyceryl monooleate	$C_{18}-H_{34}-O_2.x-(C_3H_8-O3)x-$	TOXNET[269]	Rabbit, rat	Dermal, ocular, PO
Polyvinylpyrrolidone	T90, T114; C: 216, 217, 256-258, 291-293	9003-39-8	Povidone; PVP; PVP K30	$(C_6-H_9-N-O)x-$	Beji et al[270]; PharmPK[178]; TOXNET[271]	Dog, nonhuman primate, rabbit, rat	IM, PO
Potassium chloride	T114; C: 163	7447-40-7	KCl	KCl	TOXNET[272]	Minipig	Topical
Propylene glycol	T91, T114; C: 16, 61, 65-69, 73, 98, 99, 107, 148, 153-156, 163, 190, 212-215, 234, 235, 239-255	57-55-6	1,2-Dihydroxypropane	$C_3H_8O_2$	Cavender FL[273]; Fort et al[121]; Ruble et al[108]; Thackaberry et al[155]; TOXNET[201]	Dog, minipig, guinea pig, nonhuman primate, mouse, rabbit, rat	Dermal, IP, IV, PO, SC, topical
Propylene glycol dicaprylate/dicaprate	T114; C: 127	68583-51-7	Caprylic, capric acid, propylene glycol diester	$C_{10}-H_{20}-O_2.C_8-H_{16}-O_2.C_3-H_8-O_2$	Cosmetic Ingredient Review[274]; TOXNET[275]	Rat	Topical
Propylparaben	T114; C: 128, 147, 174	94-13-3	4-Hydroxybenzoic acid, propyl ester	$C_{10}-H_{12}-O_3$	TOXNET[276]	Minipig	SC, topical
PVP VA 64	T114; C: 223, 224, 294	25086-89-9	Vinylpyrrolidone-vinyl acetate copolymer; copovidone; PVP VA	$(C_6-H_9-N-O.C_4-H_6-O_2)x-$	TOXNET[277]	Dog, rat	PO
RAMEB	T92; -		Randomly methylated-β-cylodextrins		Challa et al[36]	Nonhuman primate	Intranasal
Safflower oil	T93; -	8001-23-8	Carthamus tinctorius oil	Natural product	TOXNET[278]	Dog	SC
Salicylic acid	T114; C: 61	69-72-7	Benzoic acid, 2-hydroxy-	$C_7-H_6-O_3$	TOXNET[279]	Minipig	Topical
Saline (pH adjusted, pH 4.5)	T94; -					Mouse	IM
Sesame oil	T95, T114; C: 259, 260	8008-74-0	Gingilli oil; gingelly oil; til oil	Natural product	Farber et al[280]; Genovese et al[281]; Prasamthi et al[282]; TOXNET[283]	Dog, mouse, rabbit, rat	PO
Shea butter	T114; C: 174	194043-92-0		Natural product	TOXNET[284]	Minipig	Topical
Simethicone	T114; C: 126, 143	8050-81-5	Silicone antifoam agent S 184; Gas-x	N/A	TOXNET[285]	Rat	PO
Sodium acetate	T114; C: 92, 93, 261-265, 299, 300	127-09-3	Acetic acid sodium salt	$C_2H_3NaO_2$	TOXNET[286]	Dog, mouse, nonhuman primate, rat	IV, PO, SC
Sodium acetate trihydrate buffer	T96, T114; C: 266, 267	6131-90-4				Mouse, nonhuman primate	IV, PO
Sodium chloride	T97, T114; C: 41, 49, 58-60, 64, 80, 96, 97, 117, 121, 148-163, 166, 189, 210, 211, 232, 236, 237, 251-253, 265, 268, 271, 273, 278-281, 285, 289	7467-14-5	Salt; saline; halite	NaCl	Barrie et al[287]; Caraccio et al[288]; Meneely et al[289]; Meneely et al[290]; Moore et al[291]	Cat, dog, minipig, mouse, nonhuman primate, rabbit, rat	ID, IP, IM, IV, ocular, perivascular, PO, SC, topical
Sodium citrate	T114; C: 251-258, 268, 294, 303	994-36-5		$C_6-H_8-O_7.x-Na$	TOXNET[292]	Nonhuman primate, rat	IV, PO
Sodium dihydrogen phosphate dihydrate	T98, T114; C: 42	13472-35-0	Sodium phosphate, monobasic, dihydrate; SDPD	$H_2-O_4-P.Na.2H_2-O$	TOXNET[293]	Mouse, nonhuman primate	PO, SC

(continued)

Table 4 (continued)

Excipient/vehicle	Data in table # (T#); combination: # (C#)	CAS#	Synonyms	Formula	Key toxicity review articles/sources	Animal species evaluated	Administration routes evaluated
Sodium hydroxide	T114; C: 147, 163, 234, 235, 271, 272, 277, 304	1310-73-2	Caustic soda	NaOH	TOXNET[294]	Minipig, mouse, nonhuman primate, rat	IV, SC, topical
Sodium lauryl sulfate	T114; C: 142-146	151-21-3	Sodium dodecyl sulfate	C_{12}-H_{26}-O_4-S.Na	TOXNET[295]	Dog, rat	PO
Sodium metabisulfite	T99; -	7681-57-4			TOXNET[296]	Mouse, nonhuman primate, rat	PO
Sodium methylparaben	T114; C: 269, 270	5026-62-0	Benzoic acid, 4-hydroxy-, methyl ester, sodium salt	C_8-H_7-Na-O_3	TOXNET[297]	Minipig, mouse, rat	PO, topical
Sodium phosphate buffer	T100, T114; C: 121, 273-277, 289	7558-80-7			Jefferson[298]; Moore et al[291]; TOXNET[299]	Dog, mouse, nonhuman primate, rat	IV, PO
Sodium propylparaben	T114; C: 269, 270	35285-69-9	4-Hydroxybenzoic acid, propyl ester, sodium salt	C_{10}-H_{11}-Na-O_3	TOXNET[300]	Mouse, rat	PO
Sodium succinate	T114; C: 118, 122, 123, 278-282	150-90-3	Succinic acid sodium salt; succinic acid; disodium butanedioate	$C_4H_4Na_2O_4$	Szilagyi[301]; TOXNET[302]	Dog, mouse, rat	IV, SC
Sodium sulfite	T101; -	7757-83-7	Sulfurous acid, disodium salt	H_2-O_3-S.2Na; O_3-S.2Na	TOXNET[303]	Rabbit	Ocular (topical)
Solutol HS 15 (see also: Kolliphor HS 15)	T102, T114; C: 55, 70, 71, 218-222, 283-286	61909-81-7	Polyethylene glycol-15-hydroxystearate; polyethylene glycol 660 hydroxy stearate	$(C_2$-H_4-$O)$mult-C_{18}-H_{36}-O_3	Cavender[128]; Coon et al[304]; Dordunoos et al[129]; Ruchatz[305]; Stokes et al[180]; TOXNET[306]	Dog, mouse, nonhuman primate, rat	IV, IP, PO, any
Sorbitan tristearate	T114; C: 174	26658-19-5	Sorbitan, trioctadecanoate	C_{60}-H_{114}-O_8	Lanigan and Yamarik[307]; TOXNET[308]	Minipig	Topical
Sorbitol	T114; C: 287, 299, 300	50-70-4	D-Sorbitol	C_6-H_{14}-O_6	TOXNET[309]	Dog, nonhuman primate, rat	IV
Soybean oil	T 103, T114; C: 288	8001-22-7		Natural product	Cambridge MedChem[310]; Earl et al[311]; Farber et al[280]; Kawashima et al[312]; TOXNET[313]	Dog, minipig, rat	PO, topical
Squalene NF	T114; C: 163	111-02-4		C_{30}-H_{50}	TOXNET[314]	Minipig	Topical
Stearic acid	T114; C: 288	57-11-4	N-Octadecanoic acid	C_{18}-H_{36}-O_2	TOXNET[315]	Minipig	Topical
Stearyl alcohol	T114; C: 288	112-92-5	1-Octadecanol	C_{18}-H_{38}-O	TOXNET[316]	Minipig	Topical
Sucrose	T114; C: 42, 78, 79, 274, 275, 289	57-50-1	Sugar	C_{12}-H_{22}-O_{11}	TOXNET[317]	Cat, dog, nonhuman primate, rabbit, rat	IV, PO mucosa, PO, SC
Sucrose acetate isobutyrate	T114; C: 290	27216-37-1	Sucrose acetate isobutyrate (SAIB)	C_{40}-H_{62}-O_{19}	TOXNET[318]	Cat	PO mucosa
Sulfobutylether β-cyclodextrin	T104; -	182410-00-0	Sulfobutylether-β-cyclodextrin (SBECD)	N/A	Albers and Muller[35]; Challa et al[36]; Kim et al[319]; Marttin et al[37]; TOXNET[320]; Ueda et al[321]	Mouse	PO
Tartaric acid	T105; -	87-69-4	D-Tartaric acid; 2,3-dihydroxybutanedioic acid	C_4-H_6-O_6	Sourkes and Koppanyi[322]; Szilagyi[323]; TOXNET[324]	Rabbit, rat	PO
Terbinafine HCl placebo nail lacquer	T106; -	78628-80-5	Terbinafine hydrochloride	C_{21}-H_{25}-NCl-H	TOXNET[325]	Pig	Dermal
Tetraglycol	T114; C: 56, 157, 158	15826-19-4			TOXNET[326]	Minipig, rat	IV
Transcutol	T107, T114; C: 75-77, 113, 114	111-90-0	Diethylene glycol monoethyl ether; DEGEE; 2-(2-ethoxyethoxy)ethanol	$C_6H_{14}O_3$	Liu et al[327]; Sullivan et al[328]; TOXNET[98]	Cat, dog, guinea pig, minipig, mouse, rabbit, rat	Dermal, IM, IP, IV, inhalation, ocular, PO, SC
Trehalose	T114; C: 39, 296-298	99-20-7	α-D-Trehalose	C_{12}-H_{22}-O_{11}	TOXNET[329]	Dog, rat	IA, IV

(continued)

Table 4 (continued)

Excipient/vehicle	Data in table # (T#); combination: # (C#)	CAS#	Synonyms	Formula	Key toxicity review articles/sources	Animal species evaluated	Administration routes evaluated
Tris buffer	T114; C: 52	77-86-1	Tromethamine	C_4-H_{11}-N-O_3	TOXNET[330]	Minipig, nonhuman primate	IV, topical
Trisodium citrate dihydrate	T108; -	6132-04-3	Trisodium citrate; sodium citrate	$C_6H_5Na_3O_7 \cdot 2H_2O$	TOXNET[292]	Dog, hamster, mouse, rat	PO
Tween 20	T109, T114; C: 18, 19, 61, 163, 225-228, 273, 299, 300	9005-64-5	Polysorbate 20 NF	N/A	Bartsch et al[104]; TOXNET[331]	Dog, minipig, mouse, nonhuman primate, rat	IV/SC/IP, IV, PO, SC, topical
Tween 80	T110, T114; C: 6, 7, 20-30, 57, 81, 82, 86, 90, 100, 101, 103-105, 107, 112, 120, 125, 129-141, 159, 174, 176, 175, 213-215, 229, 230, 232, 266, 267, 287, 301, 302, 305	9005-65-6	Polysorbate 80; Armotan PMO-20, Tween 80; polyoxyethylene (20) sorbitan monooleate	N/A	Daher et al[332]; Fisherman and Cohen[333]; Gelperina et al[334]; National Toxicology Program[335]; O'Sullivan et al[336]; Oz et al[337]; Sellers et al[215]; Thackaberry et al[155]; TOXNET[338]	Dog, guinea Pig, hamster, minipig, mouse, nonhuman primate, rabbit, rat	IA, IV/SC/IP, intranasal, IV, IP, PO, SC, topical
Vitamin E	T114; C: 167-169, 303	59-02-9	α-Tocopherol	C_{29}-H_{50}-O_2	TOXNET[339]	Dog, rabbit, rat	Ocular, PO
Vitamin E TPGS	T111, T114; C: 107, 176, 177, 216, 217, 223, 224, 227, 228, 255, 291-295	9002-96-4	Tocophersolan (USAN)	$(C_2$-H_4-$O)$mult-C_{33}-H_{54}-O_5 $(C_2$-H_4-$O)$n-C_{33}-H_{54}-O_5	TOXNET[340]	Dog, mouse, rabbit, rat	PO
Water (note: only combination formulations expressly listing water in their ingredients are listed here)	T112, T114; C: 1, 17, 23-27, 42, 53-55, 58, 61-63, 65-72, 74, 80, 86, 87, 90-94, 98-101, 108-111, 118, 121, 122-125, 138-141, 143-146, 163, 174, 190, 191, 200-205, 212-215, 234, 235, 241-250, 261-264, 273-275, 278-283, 286, 287, 289, 291-295, 301, 304, 305	7732-18-5		H_2O		Dog, guinea pig, minipig, mouse, nonhuman primate, pig, rabbit, rat	Dermal, IA/SC, IP, IV, PO, SC, topical
White wax	T114; C: 288	8012-89-3	Beeswax	Natural product	Carlton et al[222]; TOXNET[341]	Minipig	Topical
Xylitol	T113; -	87-99-0	Xylite	C5H12O5	Takahashi et al[342]; TOXNET[343]	Nonhuman primate	Intranasal

Abbreviations: BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene; CAS, Chemical Abstracts Service; CMC, carboxymethylcellulose; DAM, diacetylmonoxime; DMA, dimethyl acetamide; DMSO, dimethylsulfoxide; EDTA, ethylenediaminetetraacetic acid; EP, European Pharmacopeia; HPMC, hydroxypropyl methylcellulose; IA, intra-articular; IM, intramuscular; IP, intraperitoneal; IV, intravenous; NF, National Formulary; NMP, N-Methyl-2-pyrrolidone; PBS, phosphate-buffered saline; PEG, polyethylene glycol; PET, polyethylene terephthalate; PO, oral; PVP VA, polyvinylpyrrolidone/vinyl acetate; RAMEB, Randomly methylated β-cyclodextrin; SC, subcutaneous; TPGS, D-α-tocopheryl polyethylene glycol succinate; USP, United States Pharmacopeia.

Table 5. Acacia.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Nonhuman primate	PO	Efficacy	100 mg/kg/d	Well tolerated; some weight loss, reduction in food intake	Arabic gum; 3% solution in water	Gad et al[2]
Rat	PO	1 month	500 mg/kg	Well tolerated		Gad et al[2]
	PO	90 days	10 mL/kg	Well tolerated	20% solution	Gad et al[2]

Abbreviation: PO, oral.

Table 6. Acetic Acid.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Mouse	PO	1 month	5 mL/kg	Well tolerated	15% solution	Gad et al[2]
	PO (gavage)	90 days	5 mL/kg	Well tolerated	3% solution	Gad et al[2]
Rat	PO	Acute	5 mL/kg	Well tolerated	10% solution	Gad et al[2]
	PO	1 month	10 mL/kg	Well tolerated	20% solution	Gad et al[2]
	PO (gavage)	90 days	5 mL/kg/d	Well tolerated	3% in purified water (92/8)	Gad et al[2]

Abbreviation: PO, oral.

Table 7. Acetone.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Guinea pig	Dermal	1 month	1 mL	Well tolerated		Gad et al[2]
Mouse	Dermal	2 year	0.5 mL	Well tolerated		Gad et al[2]
	PO	2 weeks	3 mL/kg	Higher doses cause acidosis; transient neurobehavioral effects at this dose		Gad et al[2]
Rabbit	Dermal	90 days	1 mL	Defatting of application site		Gad et al[2]
Rat	Dermal	30 days	5 mL/kg	Well tolerated		Gad et al[2]
	Dermal	90 days	1.5 mL/kg 6 hours daily, 5 d/wk	Well tolerated	Sham treatment group included, vehicle similar to sham treatment; 100% acetone; age 60 days; ♂/♀	New contributed data
	PO	2 weeks	5 mL/kg	Higher doses cause acidosis; transient neurobehavioral effects at this dose		Gad et al[2]

Abbreviation: PO, oral.

Table 8. Acetylmethylamide.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Nonhuman primate	PO	1 month (ADME)		Well tolerated	In water	Contributed data, 2006

Abbreviation: ADME, absorption, distribution, metabolism, excretion; PO, oral.

Table 9. Alginic Acid.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	IP	1 month	100 mg/kg	Well tolerated		Gad et al[2]

Abbreviation: IP, intraperitoneal.

Table 10. Anecortave Acetate.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	SC (bolus)	4 doses	2 mL/kg	Well tolerated		Gad et al[2]

Abbreviation: SC, subcutaneous.

Table 11. Avicel CL-611.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO (gavage)	Single dose	1 mL/kg	Soft feces	2.4% in sterile water; age 5 months; ♂/♀	New contributed data

Abbreviation: PO, oral.

Table 12. Balanced Salt Saline.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rabbit	Intravitreal	43 days	50 μL /eye q14d	None	Non-GLP; age 5 months; 2♂/2♀	New contributed data

Abbreviations: GLP, good laboratory practice; q14d, every 14 days; SD, single dose.

Table 13. Basal Salt Solution.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Mouse	Subretinal injection	SD for 9 months	2.0 μL	None	Non-GLP; age 5-7 weeks; 44♂	New contributed data

Abbreviations: GLP, good laboratory practice; SD, single dose.

Table 14. Benzoic Acid.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	PO	Acute	100 mg/kg	Well tolerated		Gad et al[2]

Abbreviation: PO, oral.

Table 15. Beta-Cyclodextrin.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	IP	1 month	50 mg/kg	Well tolerated		Contributed data, 2006
	IV	1 month	100 mg/kg	Well tolerated		Contributed data, 2006
	PO	1 month	200 mg/kg	Well tolerated		Contributed data, 2006
Mouse	IP	1 month	10 mg/kg	Well tolerated		Contributed data, 2006
Nonhuman primate	PO	12 months		Tubular hypertrophy at doses above 100 mg/kg/d at 3 months or longer		Gad et al[2]
Rat	IV	≥3 months		Tubular hypertrophy at doses above 100 mg/kg/d at 3 months or longer		Gad et al[2]
	PO	12 month	500 g/kg	Hepatitis, nephrosis, and acute tubular necrosis at dose levels above 20 g/kg		Gad et al[2]

Abbreviations: IP, intraperitoneal; IV, intravenous; PO, oral.

Table 16. Bicarbonate Buffer, pH 9.5.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Mouse	PO (gavage)	QD for 2 months	10 mL/kg	None	Age 8-10 weeks; ♂/♀	New contributed data

Abbreviations: PO, oral; QD, once a day.

Table 17. Calcium Chloride.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Mouse	IV	1×/wk for 4 weeks	1.61 mL/kg	None	0.5 mol/L; age 5 weeks; ♂/♀	New contributed data
	SC	1×/wk for 4 weeks	1.61 mL/kg	None	0.5 mol/L; age 5 weeks; ♂/♀	New contributed data

Abbreviations: IV, intravenous; SC, subcutaneous.

Table 18. Canola Oil.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO	1 month	2 mL/kg	Well tolerated		Gad et al[2]

Abbreviation: PO, oral.

Table 19. Capryol 90.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO	28 days	1,000 mg/kg	Nontoxic		Gad et al[2]
	PO	28 days	2,500 mg/kg	Nontoxic		Gad et al[2]
Rabbit	Dermal	Acute	No dilution	Mildly irritant		Gad et al[2]
	Ocular	Acute	No dilution	Moderately irritant		Gad et al[2]
Rat	PO	Acute		Nontoxic LD_{50} > 5 g/kg		Gad et al[2]
	PO	7 days	300, 1,000, 2,500 mg/kg	Well tolerated		Gad et al[2]
	PO	28 days	500, 1,500, 2,500 mg/kg	NOAEL of 2,500 mg/kg		Gad et al[2]

Abbreviations: LD_{50}, lethal dose for 50% of population; NOAEL, no observed adverse effect level; PO, oral.

Table 20. Captisol.

Species	Route	Duration	Dose	Adverse reactions/ toxicity	Notes	Data source
Dog	PO (gavage)	2×/wk for 28 days	5 mL/kg	None	15% in DI water; age 5-6 months; ♂/♀	New contributed data
	IV (bolus)		1 mL/kg	Well tolerated	12% solution in water pH 3-11	Strickley[8]
	IV (infusion)		2 mL/kg	Well tolerated	12% solution in water pH 3-11	Strickley[8]
Mouse	PO	1 month	500 mg/kg	Well tolerated	10% solution	Gad et al[2]
	SC	90 days	1,200 mg/kg	NOEL		Gad et al[2]
	SC	6 month	1,200 mg/kg	NOAEL		Gad et al[2]
Nonhuman primate	PO	9 months	1 g/kg	Well tolerated	10% solution	Gad et al[2]
	SC	3×/wk for 12 months	120 mg/kg	Well tolerated		Gad et al[2]
Rat	IV	1 month	4 mL/kg	Well tolerated	12% in water	Gad et al[2]
	IV (bolus)		2 mL/kg	Well tolerated	12% solution in water pH 3-11	Strickley[8]
	IV (infusion)		5 mL/kg	Well tolerated	12% solution in water pH 3-11	Strickley[8]
	PO	1 month	10 mL/kg	Well tolerated	12% in water	Gad et al[2]
	PO (gavage)	2×/wk for 28 days	10 mL/kg	None	15% in DI water; age 7-8 weeks; ♂/♀	New contributed data

Abbreviations: DI, deionized; IV, intravenous; NOAEL, no observed adverse effect level; NOEL, no adverse effect level; PO, oral; SC, subcutaneous.

Table 21. Carboxymethylcellulose.

Species	Route	Duration	Dose	Adverse reactions/ toxicity	Notes	Data source
Minipig	PO	14 days	8.0 mL/kg SD	None	0.5% CMC in water; GLP; age 3 months; 1♂/1♀	New contributed data
	PO	28 days	8.0 mL/kg QD	None	0.5% CMC in water; GLP; age 3-4 months; 4♂/4♀	New contributed data
Nonhuman primate	PO	30 days		Well tolerated	5% in water	Gad et al[2]
	SC	Acute	10 mL/kg	Well tolerated		Gad et al[2]

(continued)

Table 21. (continued)

Species	Route	Duration	Dose	Adverse reactions/ toxicity	Notes	Data source
Rat	PO		20 mg/kg	NOEL	5% in water	Gad et al[2]
	PO	14 days	8.0 mL/kg SD	None	0.5% CMC in water; GLP; age 8 weeks; 5♂/5♀	New contributed data
	PO	28 days	8.0 mL/kg QD	None	0.5% CMC in water; GLP; age 8 weeks; 10♂/10♀	New contributed data
	PO (gavage)	93 weeks	10 mL/kg QD	None	1% CMC (medium viscosity) in DI water; age 6 weeks; ♂/♀	New contributed data

Abbreviations: CMC, carboxymethylcellulose; DI, deionized; GLP, good laboratory practice; NOEL, no adverse effect level; PO, oral; QD, once a day; SC, subcutaneous; SD, single dose.

Table 22. Carboxymethylcellulose Calcium.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO	90 days	1 mL/kg	Well tolerated	1% solution	Gad et al[2]

Abbreviation: PO, oral.

Table 23. Carboxymethylcellulose Sodium.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rabbit	PO	1 month	0.5 mL/kg	Well tolerated	1% solution	Gad et al[2]

Abbreviation: PO, oral.

Table 24. Cetyl Alcohol.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Mouse	IP	1 month	100 mg/kg	Well tolerated		Gad et al[2]

Abbreviation: IP, intraperitoneal.

Table 25. Citrate Buffer.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	IV infusion	8 doses	30 mL/kg/d	Well tolerated	0.1 mol/L, aqueous	Gad et al[2]
	SC	30 days	10 mL/kg QD	Well tolerated		Gad et al[2]
Rat	IV	4 weeks	ND	Hypoactivity, pain at injection site	100 mmol/L at pH 5	Contributed data, 2006
	PO	2 weeks	10 mL/kg	Well tolerated	50 mmol/L	Gad et al[2]
	PO	2 weeks	15 mL/kg	Well tolerated	50 mmol/L	Gad et al[2]

Abbreviations: IV, intravenous; ND, not determined; PO, oral; QD, once a day; SC, subcutaneous.

Table 26. Citric Acid Buffer.

Species	Route	Duration	Dose	Adverse reactions/ toxicity	Notes	Data source
Mouse	PO (gavage)	182 days	2 mL/kg QD	None	0.015 mol/L at pH 4.50; age 6-7 weeks; ♂/♀	New contributed data
Nonhuman primate	PO (gavage)	39 weeks	7.5 mL/kg QD	None	10 mmol/L; age 3-3.5 years; ♂/♀	New contributed data
Rat	PO	2 weeks	10 mL/kg QD	Well tolerated	50 mmol/L	Gad et al[2]
	PO	2 weeks	15 mL/kg QD	Well tolerated	50 mmol/L	Gad et al[2]

Abbreviations: PO, oral; QD, once a day.

Table 27. Collagen Matrix.

Species	Route	Duration	Dose	Adverse reactions/ toxicity	Notes	Data source
Nonhuman primate	Implantation in humerus bone	6 months	10 mL/kg/d	Well tolerated	Bovine type I and hydroxyapatite	Gad et al[2]
Rabbit	Implantation	6 months	Single application, 5 mL/kg	Well tolerated		Gad et al[2]

Table 28. Corn Oil.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Chicken embryo	Injection into egg	Single dose	0.1 μL/g	Less mortality than 1.0 μL/g egg		Gad et al[2]
	Injection into egg	Single dose	1.0 μL/g	Increased mortality, decreased activity during righting reflex, running time, visual discrimination, and olfactory aversion test		Gad et al[2]
Dog	PO	1 month	3.0 mL/kg	Well tolerated		Gad et al[2]
Mouse	PO	1 month	2.5 mL/kg	Well tolerated		Gad et al[2]
Nonhuman primate	PO	1 month	1 mL/kg	Well tolerated		Contributed data, 2006
Rabbit	PO	1 month	1 mL/kg	Well tolerated		Gad et al[2]
Rat	PO (gavage)	Single dose	10 mL/kg	Well tolerated		Gad et al[2]
	PO (gavage)	20 doses	5 mL/kg	Well tolerated		Gad et al[2]
	PO (gavage)	90 days	5 mL/kg QD	None	Age 6 weeks; ♂/♀	New contributed data

Abbreviations: PO, oral; QD, once a day.

Table 29. Cottonseed Oil.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	SC	Single dose	1 mL	Well tolerated; no evidence of irritation macroscopically or histologically	100% solution	New contributed data

Abbreviation: SC, subcutaneous.

Table 30. Cyclohexane.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rabbit	PO	30 days	0.5 mL/kg/d	Well tolerated		Gad et al[2]
Rat	Dermal	30 days	1 mL/kg/d	Well tolerated		Gad et al[2]
	PO (gavage)	4 weeks	5 mL/kg/d	Intermittent convulsive after dosing, piloerection round back, and emaciated appearance		Gad et al[2]

Abbreviation: PO, oral.

Table 31. Dextrose.

Species	Route	Duration	Dose	Adverse reactions/ toxicity	Notes	Data source
Cat	Oral mucosa	24 hours	0.6 mL SD	None	5%; non-GLP; age >6 months; 3♂/3♀	New contributed data
Dog	IV	Single dose	150 mL/h	Well tolerated	5%, USP	Contributed data, 2006
	IV/PO	ADME	2/10 mL/kg/d	Well tolerated	5% solution	Gad et al[2]
Nonhuman primate	PO (gavage)	13 weeks	0.78-9.3 mL/kg/d	Well tolerated	10% solution (wt/wt)	Gad et al[2]
	PO (gavage)	ADME	5 mL/kg/d	Well tolerated	5% solution	Gad et al[2]
	PO (gavage)	Single dose	5 mL/kg	Well tolerated	5% solution	Gad et al[2]

(continued)

Table 31. (continued)

Species	Route	Duration	Dose	Adverse reactions/ toxicity	Notes	Data source
Rabbit	IV (slow bolus)	12 doses		Well tolerated	5%, USP	Contributed data, 2006
Rat	IV	Single dose	1.4 mL/animal	Well tolerated	5%, USP	Gad et al[2]
	IV	7 days	5 mL/kg SD	None	5%; non-GLP; age 7-10 weeks; 2♂/2♀	New contributed data
	PO (gavage)	26 weeks	0.71-8.6 mL/kg/d	Well tolerated	10% solution (wt/wt)	Gad et al[2]
	PO (gavage)	Prelim	5 mL/kg/d	Well tolerated	5% solution	Gad et al[2]
	SC	2 weeks	0.75 mL/kg/d	Well tolerated	5% solution	Gad et al[2]

Abbreviations: ADME, absorption, distribution, metabolism, excretion; GLP, good laboratory practice; IV, intravenous; PO, oral; SC, subcutaneous; SD, single dose; USP, United States Pharmacopeia.

Table 32. Dichlorvos.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Nonhuman primate	IV Infusion	2 weeks	2 mL/kg; 10 minutes; 3×/week	Well tolerated	10 mg/mL dichlorvos; age 3-6.5 years; ♀	New contributed data

Abbreviation: IV, intravenous.

Table 33. Diethylacetamide.

Species	Route	Duration	Dose	Adverse reactions/ toxicity	Notes	Data source
Cat	IV	Single dose	1 g/kg (1,000 mg/kg)	LD_{LO}	Behavioral: altered sleep time (including change in righting reflex)	Budden et al[92]
Chicken	IV	Single dose	3,900 mg/kg	LD_{LO}		Caujolle et al[93]
Dog	IV	Single dose	1 g/kg (1,000 mg/kg)	LD_{LO}	Behavioral: altered sleep time (including change in righting reflex)	Budden et al[92]
Mouse	IP	Single dose	1,600 mg/kg	LD_{50}	Sense organs and special senses: mydriasis (pupillary dilation)	ChemIDplus[94]
	IV	Range finding	MTD: 1.4 g/kg; NOEL: 468 mg/kg		Published LD_{50} = 2.3-3.2 g/kg	Sambrone[6]
Rabbit	IV	Single dose	1,920 mg/kg	LD_{LO}		Caujolle et al[93]
Rat	IP	Single dose	1,840 mg/kg	LD_{50}		Caujolle et al[93]
	IV	Single dose	1 g/kg (1,000 mg/kg)	LD_{50}	Behavioral: altered sleep time (including change in righting reflex)	Budden et al[92]

Abbreviations: IV, intravenous; IP, intraperitoneal; LD_{50}, lethal dose for 50% of population; LD_{LO}, lowest dose causing lethality; MTD, maximum tolerated dose; NOEL, no adverse effect level.

Table 34. Diethyleneglycol-Monoethylether.

Species	Route	Duration	Dose	Adverse reactions/ toxicity	Notes	Data source
Nonhuman primate	IV	1 month (ADME)	0.355 mL/kg; single injection	Well tolerated	Into saphenous vein	Gad et al[2]

Abbreviations: ADME, absorption, distribution, metabolism, excretion; IV, intravenous.

Table 35. Dimethylacetamide.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Chicken	IV	Acute	12,000 mg/kg	LD_{Lo}	Lowest published lethal dose	Leadscope Data Portal[344]
Dog	Dermal	6 weeks	2,690.476 mg/kg QD	TD_{Lo}; fatty liver degeneration; chronic death (nutritional and gross metabolic); reproductive		Leadscope Data Portal[344]

(continued)

Table 35. (continued)

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Mouse	IP	Acute	2,800 mg/kg	LD_{50}		Leadscope Data Portal[344]
	IV	Acute	3,020 mg/kg	LD_{50}		Leadscope Data Portal[344]
	IV (into tail vein)	Acute	469 mg/kg (dose volume 5 mL/kg)	NOEL	10% solution	Thackaberry[252]
	IV (into tail vein)	Acute	1,405 mg/kg (dose volume 5 mL/kg)	MTD	30% solution; mild to moderate hypoactivity for up to 6 minutes is typical	Thackaberry[252]
	PO	Acute	4,620 mg/kg	LD_{50}	Intragastric feeding or introduction with drinking water	Leadscope Data Portal[344]
Rabbit	Dermal	Acute	2,240 mg/kg	LD_{50}	Application directly onto the skin, either intact or abraded	Leadscope Data Portal[344]
	IV	Acute	8,340 mg/kg	LD_{Lo}	Lowest published lethal dose	Leadscope Data Portal[344]
	PO	13 days	3,900 mg/kg	TD_{Lo}; specific developmental abnormalities (eye, ear, craniofacial including nose and tongue, musculoskeletal system); postimplantation mortality; fetotoxicity (except death, eg, stunted fetus)	Intragastric feeding or introduction with drinking water; 6-18 days of pregnancy	Leadscope Data Portal[344]
Rat	Inhalation	6 h/d for 10 days	281 ppm	TD_{Lo}	Inhalation in chamber by cannulation or through mask; 6-15 days of pregnancy	Leadscope Data Portal[344]
	IP		2 mg/kg	TD_{Lo}; postimplantation mortality; fetotoxicity (except death, eg, stunted fetus)	1 day pregnant	Leadscope Data Portal[344]
	IP	Acute	2,750 mg/kg	LD_{50}		Leadscope Data Portal[344]
	IV	Acute	2,640 mg/kg	LD_{50}		Leadscope Data Portal[344]
	PO	14 days	5,600 mg/kg	TD_{Lo}; effects on fertility, postimplantation mortality; fetal death; specific developmental abnormalities (craniofacial, including nose and tongue, musculoskeletal system, cardiovascular system, homeostasis); fetotoxicity (except death, eg, stunted fetus)	Intragastric feeding or introduction with drinking water; 6-19 days of pregnancy	Leadscope Data Portal[344]
	PO	14 days	2,240 mg/kg	TD_{Lo}	Intragastric feeding or introduction with drinking water; 6-19 days of pregnancy	Leadscope Data Portal[344]
	PO	Acute	4,300 mg/kg	LD_{50}	Intragastric feeding or introduction with drinking water	Leadscope Data Portal[344]
	PO	10 days	1,500 mg/kg QD	TD_{Lo}; findings in digestive system and liver; chronic	Intragastric feeding or introduction with drinking water; lowest published toxic dose	Leadscope Data Portal[344]
	PO	26 weeks	2 mg/kg QD	TD_{Lo}; enzyme inhibition, induction, or change in blood or tissue levels; liver	Intragastric feeding or introduction with drinking water; lowest published toxic dose	Leadscope Data Portal[344]
	PO	90 days	50 mg/kg QD	TD_{Lo}; changes in erythrocyte (RBC) and leucocyte (WBC) counts	Intragastric feeding or introduction with drinking water; lowest published toxic dose	Leadscope Data Portal[344]

Abbreviations: IP, intraperitoneal; IV, intravenous; LD_{50}, lethal dose for 50% of population; LD_{Lo}, lowest dose causing lethality; MTD, maximum tolerated dose; NOEL, no adverse effect level; PO, oral; QD, once a day; RBC, red blood cell; TD_{Lo}, lowest dose having toxic effect; WBC, white blood cell.

Table 36. Dimethylsulfoxide.

Species	Route	Duration	Dose	Adverse reactions/ toxicity	Notes	Data source
Dog	IV	Single dose at 0.2 mL/ min for 18.5 minutes	0.43-0.46 mL/kg	During dose administration, excessive salivation and labored respiration were noted, at 1 and 4 hours postdose	Must use IV catheter; 100% solution	New contributed data
	IV		2 mg/kg			New contributed data
	IV		2.5 g/kg	LD_{50}	Must use IV catheter; 100% solution	New contributed data
	IV	Intermittent for 4 weeks	57,600 mg/kg	LD_{50}; lowest published toxic dose, hematuria, normocytic anemia, death	Must use IV catheter	New contributed data
	IV		2,500 mg/kg	LD_{50}; cardiac changes, hematuria		New contributed data
		Single dose	1 mL/kg	Well tolerated	10% solution	New contributed data
	IV		0.1 mL/kg		Must use IV catheter; 100% solution	New contributed data
	IV	1 month	1.25 mL/(0.112) × (BW)	Well tolerated		Gad et al[2]
Guinea Pig	IV	1 month	0.1 mL/kg	Well tolerated		Gad et al[2]
	IP	Acute	6.5 g/kg	LD_{50}	100% solution	New contributed data
Mouse	IP	1 month	2.5 g/kg	LD_{50}	100% solution	New contributed data
	IP		3.82-10.73 g/kg	LD_{50}	100% solution	New contributed data
	IP		8.2 g/kg	LD_{50}	100% solution	New contributed data
	IP		20.06 g/kg	LD_{50}	100% solution	New contributed data
	IP	1 month	100 mg/kg	Well tolerated		Gad et al[2]
	IP	3 days	10 mL/kg	Well tolerated	15% solution	Gad et al[2]
	IV (into tail vein)	Acute	1,650 mg/kg (dose volume 5 mL/kg)	NOEL	30% solution	Thackaberry[252]
	IV (into tail vein)	Acute	2,200 mg/kg (dose volume 5 mL/kg)	MTD; rapid breathing, ataxia, and muscle contractions, with full recovery by 1 minute is typical	40% solution	Thackaberry[252]
	IV	Range finding	MTD: 2.2 g/kg; NOEL: 1.6 g/kg		Published LD_{50} = 3.8-7.6 g/kg	Sambrone[6]
	IV		3,100 mg/kg	LD_{50}; eye hemorrhage, conjunctiva irritation		New contributed data
	IV		240 g/kg	Lowest published toxic dose; postimplantation mortality	Age day 1-20 presumed pregnant	New contributed data
	PO (gavage)		15.0-22 g/kg	LD_{50}	100% solution	New contributed data
	PO (gavage)		7.9 g/kg	LD_{50}	100% solution	New contributed data
	PO		5 mL/kg			Gad et al[2]
	SC		13.9-20.5 g/kg	LD_{50}	100% solution	New contributed data
Nonhuman primate	PO (gavage)	Efficacy	3 mL/kg/d	Well tolerated		Gad et al[2]
Rabbit	SC	1 month	1 mL/kg	Erythema, inflammation		Gad et al[2]

(continued)

Table 36. (continued)

Species	Route	Duration	Dose	Adverse reactions/ toxicity	Notes	Data source
Rat	IV		4 to 5 mg/kg			New contributed data
	IV		5.25-5.36 g/kg	LD_{50}	100% solution	New contributed data
	IV		5.3 g/kg	LD_{50}	100% solution	New contributed data
	IV	Single dose	200 mg/kg	In serum, slightly and transiently changed metabolic parameters including glucose, lactate, triglycerides, free fatty acids, or creatinine as well as electrolytes (Na, Cl, Mg) and osmolality increased ALT and impeded clinical chemistry measurements of various parameters at 4-hour postdose; kidney function induced loss of protein and albumin	2% solution	New contributed data
	IV		5,360 mg/kg	LD_{50}; tremors, muscle weakness, dyspnea		New contributed data
	IV	1 month	200 mg/kg	Well tolerated		Gad et al[2]
	SC		12 g/kg	LD_{50}	100% solution	New contributed data
	PO (gavage)	7 days	5 mL/kg/d	Well tolerated		Gad et al[2]
	PO (gavage)	4 weeks	5 mL/kg/d	Well tolerated		Gad et al[2]
	PO (gavage)		16.0-28.3 g/kg	LD_{50}	100% solution	New contributed data
	PO (gavage)		14.5 g/kg	LD_{50}	100% solution	New contributed data
	PO (gavage)	Single dose	200 mg/kg	Did not affect stomach emptying and did not reduce intestinal transit time	2% solution	New contributed data
	PO (gavage)	Single dose	1,000 mg/kg	Did not affect stomach emptying and did not reduce intestinal transit time	10% solution	New contributed data
	IP	28 doses	5 mL/kg	Well tolerated	15% solution	Gad et al[2]
	IP		6.5-13.621 g/kg	LD_{50}	100% solution	New contributed data
	IP		8.2 g/kg	LD_{50}	100% solution	New contributed data

Abbreviations: ALT, alanine transaminase; BW, body weight; IV, intravenous; IP, intraperitoneal; LD_{50}, lethal dose for 50% of population; MTD, maximum tolerated dose; NOEL, no adverse effect level; PO, oral; SC, subcutaneous.

Table 37. Dulbecco Modified Phosphate-Buffered Saline.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	IV (into tail vein)	1 month	1 mL/kg/d	Well tolerated		Gad et al[2]

Abbreviation: IV, intravenous.

Table 38. Dulbecco Phosphate-Buffered Saline.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	PO (gavage)	1 month	0.1, 0.8, and 1.2 mg/kg/d	Well tolerated		Gad et al[2]

Abbreviation: PO, oral.

Table 39. Ethanol.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	IV		5 mL/kg at a rate of 0.3 mL/kg	Hemolysis in vitro dog blood	30% solution	New contributed data
	IV		5 mL/kg at a rate of 0.3 mL/kg	Hemolysis in vitro dog blood	40% solution	New contributed data
	IV	Single dose	1 mL/kg	Well tolerated	10% solution	New contributed data
	IV	Single dose	1 mL/kg	CNS depression, ataxia	30% solution	Gad et al[2]
	IV	5 days	1 mL/kg at 2 mL/min	Excessive salivation	30% solution; must use winged infusion set	New contributed data
	IV	At 3, 7, 14, and 24 hours after ingestion of ethylene glycol	1,584 mg/kg	Remained recumbent or severely ataxic for 36, depressed for 72	20% solution	New contributed data
	IV	Every 4 hours for 5 treatments and then every 6 hours for 4 treatments	5.5 mL/kg		20% solution	New contributed data
	PO	1 month	5 mL/kg	Well tolerated	7.5% solution	Gad et al[2]
	PO	6 months	400 mL/kg	Hepatotoxicity, myopathy, CNS changes		Gad et al[2]
	PO	90 days	5 mL/kg	Well tolerated	5% solution	Gad et al[2]
Minipig	Dermal	ADME	ND (5 mg/cm^2)	Well tolerated	60/40: purified water/ethyl alcohol absolute: vol/vol	Contributed data, 2006
Mouse	Dermal	13 weeks	100 μL/animal/d	Well tolerated	70% (62% w/w)	Gad et al[2]
	Dermal	7 days	0.5 mL (fixed volume) QD	Well tolerated	80% solution; age 6 weeks; ♂/♀	New contributed data
	IP	Acute	5 mL/kg	Well tolerated	5% solution	Gad et al[2]
	IV	Range finding	MTD: 986 mg/kg; NOEL: 197 mg/kg		Published LD_{50} = 1.6-4.3 g/kg	Sambrone[6]
	IV (into tail vein)	Acute	197 mg/kg (dose volume 5 mL/kg)	NOEL	5% solution	Thackaberry[252]
	IV (into tail vein)	Acute	986 mg/kg (dose volume 5 mL/kg)	MTD: ventral recumbency and "swimming" behavior immediately postdose, ataxia for up to 6 minutes is typical	25% solution	Thackaberry[252]
	PO	1 month	2.5 mL/kg	Well tolerated	5% solution	Gad et al[2]
	PO	6 month	2,500 g/kg	Well tolerated		Gad et al[2]
Nonhuman primate	PO	9 months	250 g/kg	Behavioral changes		Gad et al[2]
Rat	Dermal	ADME	ND (5 mg/cm^2)	Well tolerated	60/40: purified water/ethyl alcohol absolute: vol/vol	Contributed data, 2006
	Dermal	91 days	0.5 mL (fixed volume) QD	Well tolerated	80% solution; age 6 weeks; ♂/♀	New contributed data
	IP	Acute	3.75 g/kg	LD_{50}		New contributed data
	IV	Acute	1.44 g/kg	LD_{50}		New contributed data
	IV	Acute	5 mL/kg at a rate of 0.3 mL/kg	Hematuria	30% solution	New contributed data

(continued)

Table 39. (continued)

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
	IV	9 days	5 mL/kg at 2 mL/min	Ataxia, respiratory depression, and death are dosed faster than 2 mL/min	30% solution	New contributed data
	IV	12 months	250 g/kg	Nephrosis, ATN, bladder changes, weight loss		Gad et al[2]
	PO	Acute	7.06 g/kg	LD_{50}		New contributed data
	PO (gavage)	7 days	0.8, 2, and 5 mL/kg/d	Well tolerated	70% (62% w/w)	Contributed data, 2006
	PO	7 days	10 mL/kg	Well tolerated	10% solution	Gad et al[2]
	PO	Acute	5 mL/kg	Depression		Gad et al[2]
	PO (gavage)	4 weeks	2 mL/kg QD	Hypokinesia, dyspnea regurgitation, distended lungs/ileum, and swollen abdomen	70% (62% w/w)	Gad et al[2]
	PO	28 doses	175 g/kg	Depression, decreased RBC		Gad et al[2]
	PO	90 days	8 mL/kg	Well tolerated	10% solution	Gad et al[2]
	PO	12 months	1,000 mg/kg	Fatty liver		Gad et al[2]

Abbreviations: ADME, absorption, distribution, metabolism, excretion; ATN, acute tubular necrosis; CNS, central nervous system; IP, intraperitoneal; IV, intravenous; LD_{50}, lethal dose for 50% of population; MTD, maximum tolerated dose; ND, not determined; NOEL, no adverse effect level; PO, oral; QD, once a day; RBC, red blood cell.

Table 40. Gelatin Capsules.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO	5 days	QD	Well tolerated		Contributed data, 2006
	PO	6 days	QD	Well tolerated		Contributed data, 2006
	PO	8 days	QD	Well tolerated		Contributed data, 2006
	PO	14 days	QD	Well tolerated		Contributed data, 2006
	PO	16 days	QD	Well tolerated		Contributed data, 2006

Abbreviations: PO, oral; QD, once a day.

Table 41. Gelatin Phosphate Buffer.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Minipig	Topical	28 days	10 mL q14d × 2 doses	None	GLP; age 4-6 months; 5♂/5♀	New contributed data

Abbreviations: GLP, good laboratory practice; q14d, every 14 days.

Table 42. Gelucire 44/14.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO	3 months	400, 1,000, 2,500 mg/kg/d	NOAEL: >2,500 mg/kg/d		Gad et al[2]
	PO	14 days	400, 1,000, 2,500 mg/kg/d	NOAEL: >2,500 mg/kg/d		Gad et al[2]
Rabbit	Dermal	Acute	0.5 mL	Not irritant		Gad et al[2]
	Ocular	Acute	0.1 mL	Slight irritant		Gad et al[2]
Rat	PO	28 days	600, 1,500, 2,400 mg/kg/d	NOEL: 2,400 mg/kg/d		Gad et al[2]
	PO	7 days	600, 1,500, 2,400 mg/kg/d	NOEL: 2,400 mg/kg/d		Gad et al[2]
	PO	Acute	No dilution	LD_{50}: >2,004 mg/kg/d		Gad et al[2]

Abbreviations: LD_{50}, lethal dose for 50% of population; NOAEL, no observed adverse effect level; NOEL, no adverse effect level; PO, oral.

Table 43. Gelucire 50/13.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	PO	Acute		Well tolerated	No dilution; $LD_0 \geq 20{,}000$ mg/kg/d	Gattefossé Technical Document[345]

Abbreviations: LD_0, lethal dose 0%; PO, oral.

Table 44. Gluconic Acid.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO (gavage)	14 days	2 mL/kg QD	Well tolerated	0.3 mol/L gluconic acid pH 3.0; age 11 months; ♂/♀	New contributed data
Rat	PO (gavage)	14 days	10 mL/kg QD	Well tolerated	0.3 mol/L gluconic acid pH 3.0; age 10 weeks; ♂/♀	New contributed data

Abbreviations: PO, oral; QD, once a day.

Table 45. Glycerol.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	SC	28 days	20 mL/d (fixed volume)	None	2% solution in sterile water; age 5-6 months; ♂/♀	New contributed data
Guinea pig	PO	1 month	500 mg/kg	Well tolerated		Gad et al[2]
Mouse	IV	1 month	100 mg/kg	Well tolerated		Gad et al[2]
	IP	1 month	250 mg/kg	Well tolerated		Gad et al[2]
	PO	90 days	500 mg/kg	Depression and reduced respiration		Gad et al[2]
	SC	Acute	10 mg/kg	Well tolerated		Gad et al[2]
Rabbit	IV	Acute	10 mg/kg	Well tolerated		Gad et al[2]
Rat	PO	Acute	1,000 mg/kg	Well tolerated		Gad et al[2]
	PO	1 month	15 g/kg	Reduced adrenal weights		Gad et al[2]
	PO	1 month	1,000 mg/kg	Well tolerated		Gad et al[2]
	SC	Acute	10 mg/kg	Well tolerated		Gad et al[2]

Abbreviations: IP, intraperitoneal; IV, intravenous; PO, oral; SC, subcutaneous.

Table 46. Glycofurol.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	IV	Single dose	1 mL/kg	Well tolerated	50% solution	New contributed data

Abbreviation: IV, intravenous.

Table 47. Gum Tragacanth.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Mouse	PO (gavage)	2 weeks	10 mL/kg QD	Well tolerated	In distilled water, 0.5%	Gad et al[2]

Abbreviations: PO, oral; QD, once a day.

Table 48. Gum Xanthane.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rabbit	PO (gavage)	Tolerance	3 mL/kg/d	Well tolerated	0.4% aqueous solution	Contributed data, 2006
	PO (gavage)	Segment II	3 mL/kg/d	Well tolerated	0.4% aqueous solution	Contributed data, 2006

Abbreviation: PO, oral.

Table 49. Hydrochloric Acid.

Species	Route	Duration	Dose	Adverse reactions/ toxicity	Notes	Data source
Dog	PO (gavage)	4 weeks	4 mL/kg QD	None	0.1 N; age 5-6 months; ♂/♀	New contributed data
	PO (gavage)	Daily	10 mL/kg	None	0.1%-10% in water; beagles age 5 months; ♂/♀	New contributed data
Rat	PO (gavage)	26 weeks	10 mL/kg QD	None	0.05 mol/L HCl; age 6 weeks; ♂/♀	New contributed data
	PO (gavage)	Daily	10 mL/kg	None	0.1%-10% in water; age 6-8 weeks; ♂/♀	New contributed data

Abbreviations: HCl, hydrochloric acid; PO, oral; QD, once a day.

Table 50. Hydroxyethyl Cellulose.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	PO	Single dose	20 mg/kg	Intestinal transit was slightly enhanced, not dose dependent	0.5%	New contributed data
	PO	Single dose	100 mg/kg	Intestinal transit was slightly enhanced, not dose dependent	1%	New contributed data
	PO	28 days	50 mg/kg	Easiest and most tolerable formulation of PO administration		New contributed data

Abbreviation: PO, oral.

Table 51. Hydroxypropyl-β-Cyclodextrin.[a]

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	IV	1 dose	1 mL/kg	Well tolerated	40% solution	New contributed data
	IV (slow bolus)	1 dose	1.2 mL/kg	Well tolerated	6% solution	Contributed data, 2006
	IV (2-hour infusion)	1 month	10 mL/kg	Well tolerated	40% solution	Gad et al[2]
	Intranasal	14 days	1 mL/nostril TID 2 hours apart	Well tolerated	45%; beagle dogs (Marshall) age ~6 months; ♂/♀	New contributed data
	PO (gavage)	1 dose	10 mL/kg	Well tolerated	6% solution	Contributed data, 2006
	PO (gavage)	90 days	Dose volume 5 mL/kg; daily dose 500, 1,000 mg/kg	Loose/soft stools in high-dose group	Dose concentration 100, 200 mg/mL (respectively)	Thackaberry[158]
	PO (gelatin capsules)	28 doses		Emesis, fecal changes	6% solution	Contributed data, 2006
	SC	91 days	0.86 mL/kg QD	None	10% solution in sterile water; age 5.5-6 months; ♂/♀	New contributed data
Mouse	IV	Acute	5,000 mg/kg	LD	Administration directly into the vein by hypodermic needle; >5 g/kg	Leadscope Data Portal[346]
	PO (gavage)	90 days	Dose volume 10 mL/kg; daily dose 500, 1,000 mg/kg	Produced elevated transaminase (aspartate and alanine aminotransferase) levels; use with caution	Dose concentrations 50, 100 mg/mL (respectively)	Thackaberry[155]
	PO (gavage)	104 weeks	500 mg/kg/d	Well tolerated		New contributed data
Nonhuman primate	PO (gavage)	13 doses	5 mL/kg	None	11% solution	Contributed data, 2006
	PO (gavage)	90 days	Dose volume 5 mL/kg; daily dose 500, 1,000 mg/kg	Loose/soft stools in high-dose group	Dose concentration 100, 200 mg/mL (respectively)	Thackaberry[155]
	IP	Acute	10,000 mg/kg	Well tolerated, LD > 10,000 mg/kg		New contributed data
Rabbit	PO (gavage)	12 doses	2 mL/kg	Well tolerated	11% solution	Contributed data, 2006
Rat	Intranasal	14 days	50 mL/nostril TID 2 hours apart	Well tolerated	45%; Sprague Dawley (Harlan) age ~8-10 weeks at initiation; ♂/♀; histopathology limited to purulent exudates (minimal to mild) involving the nasal turbinates	New contributed data

(continued)

Table 51. (continued)

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
	IP injection	Single dose	1,000 mg/kg	Increased glucose levels at 4 hours, minor transient changes for triglycerides and BUN, no functional changes were observed, and only slight enhancement of ALT and AST	10% solution	New contributed data
	IV	Single dose	1 mL/kg	Well tolerated	20% solution	Contributed data, 2006
	IV	Single dose	10 mL/kg	Death occurred within a few minute of receiving a bolus dose of the vehicle. The rate of administration was slowed to ~2 minutes, which was tolerated, and clinical observations limited to red urine	45%; Sprague Dawley (Harlan); age ~8 weeks of age; ♂/♀	New contributed data
	IV (slow bolus)	10 doses	4 mL/kg	Well tolerated	12.5% solution	Contributed data, 2006
	IV (1-hour infusion)	1 month	10 mL/kg	Well tolerated	40% solution	New contributed data
	IV (slow bolus)		2 mL/kg	Well tolerated	12.5% solution	Contributed data, 2006
	PO	Acute	5,000 mg/kg	LD_{50} > 5,000 mg/kg		New contributed data
	PO	Single dose	Up to 2,000 mg/kg	No effect on gastric emptying, modestly inhibited intestinal transit	20% solution	New contributed data
	PO (gavage)	Single dose	10 mL/kg	Well tolerated	6% solution	Contributed data, 2006
	PO (gavage)	10 doses	10 mL/kg	Well tolerated	11% solution	Contributed data, 2006
	PO (gavage)	4 weeks	10 mL/kg QD	None	20%; age 6 weeks; ♂/♀	New contributed data
	PO (gavage)	90 days	Dose volume 5 mL/kg; daily dose 500, 1,000 mg/kg	Produced elevated transaminase (aspartate and alanine aminotransferase) levels; use with caution	Dose concentrations 100, 200 mg/mL (respectively)	Thackaberry[155]
	PO (gavage)	2 years	500 mg/kg	No effects		New contributed data
	SC	28 days	QD	Erosion/ulceration and/or necrosis generally observed. At the end of 28-day recovery period, fibrosis and subacute/ chronic inflammation at the injection sites persisted but were resolving; injection site necrosis not observed	10% HPβCD	New contributed data
	SC	91 days	QD	At the end of 28-day recovery period, fibrosis and subacute/chronic inflammation at the injection sites persisted but were resolving; injection site necrosis not observed	10% HPβCD	New contributed data
	SC	91 days	1.14 mL/kg QD	None	10% solution in sterile water; age 7 weeks; ♂/♀	New contributed data

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; HPβCD, hydroxypropyl-β-cyclodextrin; IP, intraperitoneal; IV, intravenous; LD, lethal dose; PO, oral; QD, once a day; TID, 3 times a day; SC, subcutaneous.

[a]Food and Drug Administration has informed sponsors that this excipient is no longer permitted for use in subcutaneous clinical formulations due to perceived risk of carcinogenicity[154] and has advised that it not be so used in repeat-dose nonclinical safety studies.

Table 52. Hydroxypropyl Cellulose.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	PO	90 days	1,000 g/kg	Well tolerated		Gad et al[2]

Abbreviation: PO, oral.

Table 53. Hydroxypropyl Methylcellulose.

Species	Routes	Duration	Dose	Adverse reactions/ toxicity	Notes	Data source
Dog	IP	Acute	200 mg/kg	Well tolerated		Gad et al[2]
	PO (gavage)		5 mL/kg	None	1% (methocel E5 premium LV, 5 cP) in DI water; age 6.5-7 months; ♂/♀	New contributed data
	PO (gavage)	90 days	Dose volume 5 mL/kg, daily dose 20 mg/kg (0.4% wt/vol)	Well tolerated		Thackaberry[155]
Minipig	PO (gavage)	7 days	5 mL/kg QD	None	0.5% in distilled water; age 6.5-11.5 months; ♂/♀	New contributed data
Mouse	IP	Single dose	5 mL/kg	Well tolerated	0.5%	Gad et al[2]
	IP	Acute	50 mg/kg	Well tolerated		Gad et al[2]
	PO	5 days	20 mL/kg BID	None	0.5%; non-GLP; age 9 weeks; 6♀	New contributed data
	PO (gavage)	Single dose	10 mL/kg	Well tolerated	0.5%	Gad et al[2]
	PO (gavage)	10 doses	10 mL/kg	Well tolerated	0.2%	Gad et al[2]
	PO (gavage)	90 days	Dose volume 10 mL/ kg, daily dose 20 mg/ kg (0.4% wt/vol)	Well tolerated		Thackaberry[155]
Nonhuman primate	PO (gavage)	28 days	2 mL/kg QD	None	0.5% in distilled water; age 2-3 years; ♂/♀	New contributed data
	PO (gavage)	28 days	5 mL/kg QD	Soft feces (nonadverse)	1% (Methocel E5 premium LV, 5 cP) in DI water; age 2.5-3.5 years; ♂/♀	New contributed data
	PO (gavage)	90 days	Dose volume 5 mL/kg, daily dose 20 mg/kg (0.4% wt/vol)	Well tolerated		Thackaberry[155]
	PO (gavage)	91 days	5 mL/kg QD	None	0.2% in distilled water; cynomolgus monkeys age 2 years; ♂/♀	New contributed data
Rat	IP	Single dose	5 mL/kg	Well tolerated	0.5%	Gad et al[2]
	PO (gavage)	Single dose	10 mL/kg	Well tolerated	0.2%	Gad et al[2]
	PO (gavage)	Single dose	10 mL/kg	Well tolerated	0.5%	Gad et al[2]
	PO (gavage)	90 days	Dose volume 5 mL/kg, daily dose 20 mg/kg (0.4% wt/vol)	Well tolerated		Thackaberry[155]
	PO (gavage)	91 days	5 mL/kg QD	None	1% (Methocel E5 premium LV, 5 cP) in DI water; age 6 weeks; ♂/♀	New contributed data
	PO (gavage)	Up to 104 weeks	10 mL/kg QD	None	0.2% in distilled water; age 6-11 weeks; ♂/♀	New contributed data
	PO (gavage)	182 days	10 mL/kg QD	None	0.5% in distilled water; age 6 weeks; ♂/♀	New contributed data

Abbreviations: BID, twice a day; DI, deionized; GLP, good laboratory practice; IP, intraperitoneal; PO, oral; QD, once a day.

Table 54. Hypotonic Phosphate-Buffered Saline.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	IV	2 days	2 mL/kg SD	None	GLP; age 6 months; 5♂/5♀	New contributed data
Rat	IV	2 days	2 mL/kg SD	None	GLP; age ≥8 weeks; 10♂/10♀	New contributed data

Abbreviations: GLP, good laboratory practice; IV, intravenous; SD, single dose.

Table 55. Isopropyl Alcohol.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rabbit	Dermal	1 month	1,000 g/kg	Well tolerated		Gad et al[2]

Table 56. Isopropyl Myristate.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rabbit	Dermal	1 month	500 mg/kg	Well tolerated		Gad et al[2]

Table 57. Kolliphor EL.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	IV	1 month	2 mL/kg	Well tolerated		Gad et al[2]
Rat	PO	1 month	100 mg/kg	Well tolerated		Gad et al[2]

Abbreviations: IV, intravenous; PO, oral.

Table 58. Kolliphor ELP.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog		Acute		Anaphylaxis	Up to 50%; never use for dog studies!	Xcess Biosciences[347]

Table 59. Kolliphor RH40.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	IV	1 month	2 mL/kg	Well tolerated		Gad et al[2]

Abbreviation: IV, intravenous.

Table 60. Labrafil M1944.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO	1 month	2 mg/kg	Well tolerated		Gad et al[2]
Rabbit	Dermal	Acute/PDI		Nonirritant	No dilution; 0.38 dermal irritation index	Gattefossé technical document[348]
Rat	PO	Acute	20 g/kg	Well tolerated	No dilution; $LD_0 \geq$ 20,000 mg/kg/d	Gattefossé technical document[348]

Abbreviations: LD_0, lethal dose 0%; PO, oral; PDI, Primary Dermal Irritation.

Table 61. Labrasol.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO	14 days	100, 300, 1,000, and 3,000 mg/kg/d	In high-dose group, moderate suppurative inflammation of the lungs. No adverse effects on survival and clinical observations		Gad et al[2]
	PO	13 weeks	0, 300, 1,000, and 3,000 mg/kg/d	NOEL: 1,000 mg/kg/d; NOAEL: 3,000 mg/kg/d		Gad et al[2]

(continued)

Table 61. (continued)

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rabbit	Dermal	Patch test	0.5 mL	Well tolerated		Gad et al[2]
	Ocular	Acute	0.1 mL	Slight irritant		Gad et al[2]
Rat	Dermal	Acute		Very well tolerated		Gad et al[2]
	Dermal	Patch test	0.02 mL/animal	Well tolerated		Gad et al[2]
	IV	ADME	10 mg/kg/d			Gad et al[2]
	Ocular			Slight irritant		Gad et al[2]
	PO	Acute	20, 22.4, 25.1, 28.21, and 31.60 g/kg	LD_{50} > 22 g/kg; well tolerated		Gad et al[2]
	PO	ADME	10, 150 mg/kg/d	Well tolerated		Gad et al[2]
	PO	Segment II: embryofetal development	1,000, 2,000, or 3,000 mg/kg/d	NOEL: 3,000 mg/kg/d with no indication of a teratogenicity		Gad et al[2]
	PO	14 days	100, 300, 1,000, 3,000 mg/kg/d	NOAEL: 3,000 mg/kg/d		Gad et al[2]
	PO	6 months	300, 1,000, and 3,000 mg/kg/d	NOEL: 300 mg/kg/d; NOAEL: 3,000 mg/kg/d		Gad et al[2]

Abbreviations: ADME, absorption, distribution, metabolism, excretion; IV, intravenous; LD_{50}, lethal dose for 50% of population; NOAEL, no observed adverse effect level; NOEL, no adverse effect level; PO, oral.

Table 62. Lactose.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Nonhuman primate	Inhalation	2 weeks	1 L/min/animal	Well tolerated	Lactose 200 μmol/L; anhydrous	Gad et al[2]

Table 63. Lanolin.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rabbit	Dermal	90 days	1,000 mg/kg	Well tolerated		Gad et al[2]

Table 64. Lauroglycol 90.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rabbit	Dermal	Acute	No dilution	Moderately irritant		Gad et al[2]
	Ocular	Acute	No dilution	Slightly irritant		Gad et al[2]
Rat	PO	Acute		LD_{50}: >2,003 mg/kg/d		Gad et al[2]

Abbreviations: LD_{50}, lethal dose for 50% of population; PO, oral.

Table 65. Maltitol Solution.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	IP	1 month	500 mg/kg	Well tolerated		Gad et al[2]

Abbreviation: IP, intraperitoneal.

Table 66. Maltol.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Guinea pig	PO	1 month	75 mg/kg	Well tolerated		Gad et al[2]
Rabbit	PO	1 month	100 mg/kg	Well tolerated		Gad et al[2]

Abbreviation: PO, oral.

Table 67. Mannitol.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Minipig	SC	Tolerance	0.2 mL/kg/d	Well tolerated	5% solution	Contributed data, 2006
Nonhuman primate	PO (gavage)	2 semester	10 mL/kg/d	Well tolerated		Gad et al[2]
Rabbit	IV	ADME	0.8 mL/kg	Well tolerated		Contributed data, 2006
	PO	ADME	1.6 mL/kg	Well tolerated		Contributed data, 2006

Abbreviations: ADME, absorption, distribution, metabolism, excretion; IV, intravenous; PO, oral; SC, subcutaneous.

Table 68. Methylcellulose.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	IV		40 mL	Anemia, decreased WBC, increased sedimentation rate in 24 hours	0.7%-2.8% solution	New contributed data
	PO	14 days	5.0 mL/kg QD	None	GLP; age 6 months; 6♂/6♀	New contributed data
	PO (dietary)	90 days	6%	Well tolerated		Thackaberry[155]
	PO (gavage)	14 doses	10 mL/kg/dose	Well tolerated	0.5%	Gad et al[2]
	PO (gavage)	39 weeks	5 mL/kg QD	Soft/mucoid feces	0.5% solution (400 cP) in DI water; age 6-10.5 months; ♂/♀	New contributed data
Guinea pig	PO	12 doses	4 mL/kg	Well tolerated	0.5%	Gad et al[2]
	Topical	3 weeks	0.4 mL once/wk	None	0.5% solution (400 cP) in DI water; age 2-3 months; ♂/♀	New contributed data
Mouse	PO	90 days	10 mL/kg	Well tolerated	0.5%	Gad et al[2]
Nonhuman primate	IV	30-minute infusion in a single dose	1 mL/kg	None	0.5% solution (400 cP) in DI water: ♂/♀	New contributed data
	PO (gavage)	14 doses	5 mL/kg	Well tolerated	0.5%	Gad et al[2]
	PO	1 month	10 mL/kg/dose	Well tolerated	0.5%	Gad et al[2]
	PO (gavage)	28 doses	5 mL/kg/dose	Well tolerated	1%	Gad et al[2]
	PO (gavage)	28 doses	10 mL/kg	Well tolerated	0.1%	Gad et al[2]
Rabbit	PO (gavage)	12 doses	4 mL/kg	Well tolerated	0.5%	Gad et al[2]
Rat	PO (dietary)	90 days	10%	Well tolerated		Thackaberry[155]
	PO (gavage)		1,020 mg/kg	NOAEL		Thackaberry[155]
	PO (gavage)	Single dose	10 mL/kg	None	1%	Contributed data, 2006
	PO (gavage)	Single dose	10 mL/kg	None	0.5%	Contributed data, 2006
	PO	Single dose	10 mL/kg	Well tolerated	2%	Gad et al[2]
	PO	3 days	10 mL/kg QD	None	1% solution in water; non-GLP; age 11 weeks; 5♀	New contributed data
	PO (gavage)	5 doses	10 mL/kg	None	0.5%	Contributed data, 2006
	PO (gavage)	9 doses	10 mL/kg/d	None	0.5%	Contributed data, 2006
	PO (gavage)	14 days	10 mL/kg QD	Well tolerated	1%	Gad et al[2]
	PO	1 month	10 mL/kg	Well tolerated	0.5%	Gad et al[2]
	PO	1 month	5 mL/kg	Well tolerated	0.5%	Gad et al[2]
	PO (gavage)	28 doses	5 mL/kg/dose	None	1%	Contributed data, 2006
		2 year	120 mg/kg	Well tolerated	1%	Contributed data, 2006
	PO (gavage)	182 days	10 mL/kg BID	None	0.5% solution (400 cP) in DI water; age 6 weeks; ♂/♀	New contributed data

Abbreviations: BID, twice a day; DI, deionized; GLP, good laboratory practice; IV, intravenous; NOAEL, no observed adverse effect level; PO, oral; QD, once a day; WBC, white blood cell.

Table 69. Methylpyrrolidone.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	IV	Single dose	0.25 mL/kg	Well tolerated	50% solution	New contributed data
Mouse	IV	Range finding	MTD: 1.3 g/kg; NOEL: 257 mg/kg		Published LD_{50} = 54-36,000 mg/kg	Sambrone[6]
	IV (into tail vein)	Acute	257 mg/kg (dose volume 5 mL/kg)	NOEL	5% solution	Thackaberry[252]
	IV (into tail vein)	Acute	1,285 mg/kg (dose volume 5 mL/kg)	MTD; struggling and vocalization at dosing, rapid breathing, stiff tail, and splayed limbs immediately postdose. Hypoactivity for up to 15 minutes is typical	25% solution	Thackaberry[252]

Abbreviations: IV, intravenous; LD_{50}, lethal dose for 50% of population; MTD, maximum tolerated dose; NOEL, no adverse effect level.

Table 70. Mineral Oil.

Species	Route	Duration	Dose	Adverse reactions/ toxicity	Notes	Data source
Cat	Topical	2×/wk × 2 doses for 28 days	1.15 mL total; 0.35 mL, then 0.4 mL every 60 minutes after initial application for 2 doses	None	GLP; age 54-57 days; 6♂/6♀	New contributed data
	Topical	q14d for 56 days	2.1 mL total; 0.5 mL, then 0.4 mL every 30 minutes after initial application for 4 applications	None	GLP; age 9 weeks; 6♂/6♀	New contributed data
Dog	PO	1 month	2.5 mL/kg	Well tolerated		Gad et al[2]
Guinea pig	Topical	28 days	0.4 mL q7d	None	GLP; age 6 weeks; 11♀	New contributed data
Mouse	PO	1 month	250 mg/kg	Well tolerated		Gad et al[2]
Rat	PO	1 month	5 mL/kg	Well tolerated		Gad et al[2]

Abbreviations: GLP, good laboratory practice; PO, oral; q14d, every 14 days; q7d, every 7 days.

Table 71. Olive Oil.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	PO (gavage)	28 days	10 mL/kg QD	Well tolerated	Age 6 weeks; ♂/♀	New contributed data

Abbreviations: PO, oral; QD, once a day.

Table 72. Peanut Oil.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	PO	1 month	10 g/kg	Well tolerated		Gad et al[2]
	PO	12 months	10 g/kg	Well tolerated		Gad et al[2]
	PO	90 days	10 g/kg	Well tolerated		Gad et al[2]
	PO (gavage)		5 mL/kg/d	Well tolerated		Contributed data, 2006
	SC		2 mL/kg/d	Well tolerated		Contributed data, 2006

Abbreviations: PO, oral; SC, subcutaneous.

Table 73. PEG 200.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Nonhuman primate	PO (gavage)	14 days	5 mL/kg QD	Soft/watery feces (nonadverse)	Age 2-3.5 years; ♂/♀	New contributed data
Rabbit	IV	Acute	>10 g/kg BW	LD_{50}		Smyth et al[242]

(continued)

Table 73. (continued)

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	IP		8-9 g/kg BW	LD_{50}		Quadbeck[244]
	PO (dietary)	90 days	20, 40, 80, 160, 240 g/kg diet QD (1.5, 3, 6, 12, 18 g/kg BW QD)	NOAEL = 6 g/kg BW QD	At 12 and 18 g/kg BW, liver and liver/kidney weights increased (respectively); 5♂/5♀	Smyth et al[243]
	PO (drinking water)	90 days	4.8 g/kg BW QD	NOAEL	5♂	Smyth et al[241]
	PO (drinking water)	90 days	10.9 g/kg BW QD	66% mortality; decreased body weight gain	5♂	Smyth et al[241]

Abbreviations: BW, body weight; IP, intraperitoneal; IV, intravenous; LD_{50}, lethal dose for 50% of population; NOAEL, no observed adverse effect level; PEG, polyethylene glycol; PO, oral; QD, once a day.

Table 74. PEG 300.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO (gavage)	28 days	1 mL/kg BID	None	Age 5.5-6 months; ♂/♀	New contributed data
Guinea pig	IV	1 month	1 mL/kg	Well tolerated		Gad et al[2]
Mouse	PO (gavage)	ADME	10 mL/kg/d	Well tolerated		Gad et al[2]
Rabbit	PO	1 month	500 g/kg	Well tolerated		Gad et al[2]
	IV	Acute	>10 g/kg BW	LD_{50}		Smyth et al[242]
Rat	IP	Acute	16-18 g/kg BW	LD_{50}		Quadbeck[244]
	IP	Acute	17 g/kg BW	LD_{50}		Smyth et al[242]
	IV	Acute	8 g/kg BW	LD_{50}		Carpenter and Shaffer[246]
	IV	Acute	7.1 g/kg BW	LD_{50}		Rowe and Wolf[247]
	PO (dietary)	90 days	20, 40, 80, 160, 240 g/kg diet QD (1.5, 3, 6, 12, 18 g/kg BW QD)	NOAEL = 3 g/kg BW QD	At 6, 12, 18 g/kg BW decreased body weight gain, liver and kidney weight increase, and both decreased body weight gain and increased liver weight (respectively); 5♂/5♀	Smyth et al[243]
	PO (drinking water)	90 days	5.4 g/kg BW QD	NOAEL	5♂	Smyth et al[241]
	PO (drinking water)	90 days	20.5 g/kg BW QD	66% mortality; decreased body weight gain; liver and kidney changes	5♂	Smyth et al[241]
	PO (gavage)	2 weeks	7.5 mL/kg QD or 2.5 mL/kg TID	Well tolerated	50%	Contributed data, 2006
	PO (gavage)	4 weeks	5 mL/kg/d	Well tolerated	50%	Contributed data, 2006
	PO (gavage)	28 days	2 mL/kg BID	None	Age 8 weeks; ♂/♀	New contributed data

Abbreviations: ADME, absorption, distribution, metabolism, excretion; BID, twice a day; BW, body weight; IP, intraperitoneal; IV, intravenous; LD_{50}, lethal dose for 50% of population; NOAEL, no observed adverse effect level; PEG, polyethylene glycol; PO, oral; QD, once a day; TID, 3 times a day.

Table 75. PEG 400.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	IV	Single dose	Total dose <2 g/kg		100%	New contributed data

(continued)

Table 75. (continued)

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
	IV	28 days	2-3 g/kg	Decreased blood pressure and reversible depression in respiration. These symptoms increased at doses of 3 g/kg or greater and eventually resulted in complete respiratory arrest. At necropsy, dogs were found to have pulmonary edema and small infarcts in the lungs but no changes in the heart or kidneys	100%	New contributed data
	IV				NS solution; hemolysis occurs >33% (vol/vol) concentration	Li et al[250]
	IV	Single dose	1 mL/kg	Well tolerated	30%	New contributed data
	IV	30 days, +21-day recovery	8.45 g/kg QD	Dry mouth and dry nasal mucous membrane; histopathological change in kidney; reversible cloudy swelling of kidney cells and increased glomerular volume	NS solution 25% (vol/vol)	Li et al[250]
	IV	30 days, +21-day recovery	5 mL/kg/d	Dry mouth and dry nasal mucous membrane	NS solution 25% (vol/vol)	Li et al[250]
	IV	30 days, +21-day recovery	4.23 g/kg QD	Increased values of electrolytes (Na^+ and Cl^-)	NS solution 25% (vol/vol)	Li et al[250]
	IV (bolus)		1 mL/kg	Well tolerated	60% solution in water pH 3-11	Strickley[8]
	IV (infusion)		2 mL/kg	Well tolerated	60% solution in water pH 3-11	Strickley[8]
	IV (infusion)		0.5 mL/kg	Well tolerated	80% solution in water pH 3-11	Strickley[8]
	PO (dietary)	1 year	20 g/kg diet QD (0.5 g/kg BW QD)	NOAEL = 0.5 g/kg BW QD	3♂/1♀	Smyth et al[243]
	PO (gavage)	28 days	0.25 mL/kg QD	Soft/watery feces (nonadverse)	Age 5-5.5 months; ♂/♀	New contributed data
Guinea pig	PO	1 month	1,000 mg/kg	Well tolerated		Gad et al[2]
Minipig	Dermal	2 weeks	2.5 mL/kg	Well tolerated		Gad et al[2]
	Topical	90 days	2 mL/kg QD	Mild dose site inflammation after >30 days of administration	GLP; age 4-6 months; 6♂/6♀	New contributed data
Mouse	IP	3 days	10 mL/kg	Well tolerated	35%	Gad et al[2]
	IP	1 month	2.5 mL/kg	Well tolerated	40% solution	Gad et al[2]
	IP	28 doses	500 mg/kg	Well tolerated		Gad et al[2]
	IP		14.5 g/kg BW	LD_{50}		Bartsch et al[104]
	IP		9.2 g/kg BW	LD_{50}		Shideman and Procita[251]
	IV		8.6 g/kg BW	LD_{50}		Bartsch et al[104]
	IV	Range finding	MTD: 4.5 g/kg; NOEL: 1.7 g/kg		Published LD_{50} = 8.6-9.7 g/kg	Sambrone[6]
	IV (into tail vein)	Acute	1,692 mg/kg (dose volume 5 mL/kg)	NOEL	30% solution	Thackaberry[252]
	IV (into tail vein)	Acute	4,512 mg/kg (dose volume 5 mL/kg)	MTD; tremors, ventral recumbency, and splayed limbs shortly after dosing, hypoactivity for up to 12 minutes is typical	80% solution	Thackaberry[252]

(continued)

Table 75. (continued)

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
	PO (gavage)	4 weeks	10 mL/kg/d	Well tolerated		Gad et al[2]
	PO	13 weeks	5 mL/kg BID	Well tolerated	100%; CD-1 (Harlan); age ~7 weeks at study initiation; ♂/♀	New contributed data
Nonhuman primate	PO (gavage)	28 days	1 mL/kg QD	Soft/watery feces (nonadverse)	In DI water; age 1-2 years; ♂/♀	New contributed data
	PO (gavage)	28 days	5 mL/kg QD	Soft/watery feces (nonadverse)	In DI water; age 1-2 years; ♂/♀	New contributed data
Rabbit	IV		>10 g/kg BW	LD_{50}		Smyth et al[242]
Rat	Dermal	13 weeks	2.5 mL/kg/d	Well tolerated		Gad et al[2]
	Dermal	104 weeks	2.5 mL/kg/d	Well tolerated		Gad et al[2]
	IP		14.7 g/kg BW	LD_{50}		Bartsch et al[104]
	IP		12.3 g/kg BW	LD_{50}		Rowe and Wolf[247]
	IP	1 month	5 mL/kg	Well tolerated	35%	Gad et al[2]
	IV		4.7 g/kg BW	LD_{50}		Rowe and Wolf[247]
	IV	Single dose	0.5 mL/kg	Well tolerated		Gad et al[2]
	IV (bolus)		2 mL/kg	Well tolerated	60% solution in water pH 3-11	Strickley[8]
	IV (infusion)		5 mL/kg	Well tolerated	60% solution in water pH 3-11	Strickley[8]
	PO (gavage)		2 mL/kg	Well tolerated		Gad et al[2]
	PO (gavage)	Single dose	5 mL/kg	Well tolerated		Gad et al[2]
	PO (gavage)	10 doses	1.67 mg/kg	Well tolerated		Gad et al[2]
	PO	1 month	5 mL/kg	Well tolerated		Gad et al[2]
	PO (gavage)	4 weeks	5 mL/kg/d	Well tolerated		Gad et al[2]
	PO (gavage)	28 days	3 mL/kg QD	None	Age 6 weeks; ♂/♀	New contributed data
	PO (gavage)	28 days	10 mL/kg QD	None	In DI water; age 6 weeks; ♂/♀	New contributed data
	PO	13 weeks	10 mL/kg/d	Loose feces and decreased food consumption; increased water consumption; increases in relative kidney weights; reversible renal toxicity		Li et al[250]
	PO	26 weeks	5 mL/kg BID	Well tolerated	100%; Sprague Dawley (Harlan) age ~8 weeks at initiation; ♂/♀	New contributed data
	PO (dietary)	90 days	20, 40, 80, 160, 240 g/kg diet QD (1.5, 3, 6, 12, 18 g/kg BW QD)	NOAEL = 6 g/kg BW QD	At 12, 18 g/kg BW decreased body weight gain and liver and kidney weight increase (respectively); 5♂/5♀	Smyth et al[243]
	PO (dietary)	2 years	10, 20, 40, 80 g/kg diet QD (0.75, 1.5, 3, 6 g/kg BW QD)	NOAEL = 1.5 g/kg BW QD	From 3 g/kg BW decreased BW gain (male); 20♂/20♀	Smyth et al[243]
	PO (drinking water)	90 days	4.8 g/kg BW QD	NOAEL	5♂	Smyth et al[241]
	PO (drinking water)	90 days	16.4 g/kg BW QD	66% mortality, decreased BW gain	5♂	Smyth et al[241]

Abbreviations: BID, twice a day; BW, body weight; DI, deionized; IP, intraperitoneal; IV, intravenous; LD_{50}, lethal dose for 50% of population; MTD, maximum tolerated dose; NOAEL, no observed adverse effect level; NOEL, no adverse effect level; NS, nonsterile; PEG, polyethylene glycol; PO, oral; QD, once a day; GLP, good laboratory practice.

Table 76. PEG 600.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	IP		14.1 g/kg BW	LD_{50}		Rowe and Wolf [247]
	IV		7.7 g/kg BW	LD_{50}		Pfordte[253]
	PO (dietary)	90 days	20, 40, 80, 160, 240 g/kg diet QD (1.5, 3, 6, 12, 18 g/kg BW QD)	NOAEL = 6 g/kg BW QD	From 12 g/kg BW decreased body weight gain and increased kidney weights; 5♂/5♀	Smyth et al[243]

Abbreviations: BW, body weight; IP, intraperitoneal; IV, intravenous; LD_{50}, lethal dose for 50% of population; NOAEL, no observed adverse effect level; PEG, polyethylene glycol; PO, oral; QD, once a day.

Table 77. PEG 810.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	IV		13 g/kg BW	LD_{50}		Käber[254]
	SC		16 g/kg BW	LD_{50}		Käber[254]

Abbreviations: BW, body weight; IV, intravenous; LD_{50}, lethal dose for 50% of population; PEG, polyethylene glycol; SC, subcutaneous.

Table 78. PEG 1,000.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Mouse	IP		2 g/kg BW	LD_{50}		Shideman and Procita[251]
Rabbit	IV	Acute	>10 g/kg BW	LD_{50}		Smyth et al[242]
Rat	IP	Acute	15.6 g/kg BW	LD_{50}		Smyth et al[242]
	PO (dietary)	90 days	20, 40, 80, 160, 240 g/kg diet QD (1.5, 3, 6, 12, 18 g/kg BW QD)	NOAEL = 6 g/kg BW QD	From 12 g/kg BW decreased body weight gain; 5♂/5♀	Smyth et al[242]

Abbreviations: BW, body weight; IP, intraperitoneal; IV, intravenous; LD_{50}, lethal dose for 50% of population; NOAEL, no observed adverse effect level; PEG, polyethylene glycol; PO, oral; QD, once a day.

Table 79. PEG 1,500.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	IP		17.7 g/kg BW	LD_{50}		Smyth et al[242]
	IV		8.5 g/kg BW	LD_{50}		Rowe and Wolf[247]
	PO (dietary)	90 days	0.88, 4.05, 8.1, 22.9 g/kg BW QD	NOAEL = 2 g/kg BW QD	From 4.05 g/kg BW kidney damage	Smyth et al[256]
	PO (drinking water)	90 days	20, 40, 80, 160, 240 g/kg diet QD (1.5, 3, 6, 12, 18 g/kg BW QD)	NOAEL = 3 g/kg BW QD	From 6 g/kg decreased BW gain; at 18 g/kg BW increased kidney weights; 5♂/5♀	Smyth et al[243]
	PO (drinking water)	2 years	0.2, 0.8, 4, 20 g/L QD (0.015, 0.059, 0.27, 1.69 g/kg BW QD)	1.69 g/kg BW QD: no effects on fertility, survival, hematology, or histopathology	8♂/8♀	Smyth et al[255]; Smyth et al[242]

Abbreviations: BW, body weight; IP, intraperitoneal; IV, intravenous; LD_{50}, lethal dose for 50% of population; NOAEL, no observed adverse effect level; PEG, polyethylene glycol; PO, oral; QD, once a day.

Table 80. PEG 1,540.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO (dietary)	1 year	20 g/kg diet QD (0.5 g/kg BW QD)	NOAEL = 0.5 g/kg BW QD		Smyth et al[243]
Rabbit	IV	Acute	>10 g/kg BW	LD_{50}		Smyth et al[242]

(continued)

Table 80. (continued)

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	IP	Acute	15.4 g/kg BW	LD_{50}		Smyth et al[242]
	PO (dietary)	90 days	20, 40, 80, 160, 240 g/kg diet QD (1.5, 3, 6, 12, 18 g/kg BW QD)	NOAEL = 3 g/kg BW QD	From 6 g/kg BW decreased BW gain; from 18 g/kg BW increased kidney weights; 5♂/5♀	Smyth et al[243]
	PO (dietary)	2 years	0.2, 0.8, 4, 20, 40, 80 g/kg diet QD (0.015, 0.06, 0.3, 1.5, 3, 6 g/kg BW QD)	NOAEL = 3 g/kg BW QD	From 6 g/kg QD cloudy swelling in the liver; 35♂/35♀	Smyth et al[243]

Abbreviations: BW, body weight; IP, intraperitoneal; IV, intravenous; LD_{50}, lethal dose for 50% of population; NOAEL, no observed adverse effect level; PEG, polyethylene glycol; PO, oral; QD, once a day.

Table 81. PEG 4,000.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO (dietary)	1 year	20 g/kg diet QD (0.5 g/kg BW QD)	NOAEL = 0.5 g/kg BW QD		Smyth et al[243]
Mouse	IP		8.0 g/kg BW	LD_{50}		Shideman and Procita[251]
Rabbit	IV	Acute	>10 g/kg BW	LD_{50}		Smyth et al[242]
	PO (gavage)	5 weeks (6 d/wk)	5, 10, 20 g/kg BW QD	From 5 g/kg BW decreased BW gain, decreased glycogen storage; from 20 g/kg bw decreased BWs		Smyth et al[256]
Rat	IP	Acute	11.6-13 g/kg BW	LD_{50}		Smyth et al[242]
	IP		9.7 g/kg BW	LD_{50}		Rowe and Wolf[247]
	IV		7.5 g/kg BW	LD_{50}		Rowe and Wolf[247]
	PO (dietary)	90 days	20, 40, 80, 160, 240 g/kg diet QD (1.5, 3, 6, 12, 18 g/kg BW QD)	NOAEL = 3 g/kg BW QD	From 6 g/kg BW decreased BW gain; from 12 g/kg BW increased kidney weights; 5♂/5♀	Smyth et al[243]
	PO (dietary)	90 days	1.6 g/kg BW QD	NOAEL = 1.6 g/kg BW QD		Smyth et al[242]
	PO (dietary)	2 years	0.375, 0.75, 1.5, 3, 6 g/kg BW QD	NOAEL = 3 g/kg BW QD	At 6 g/kg BW decreased BW gain; 20♂/20♀	Smyth et al[243]
	PO (drinking water)	90 days	0.04-19 g/kg BW QD	NOAEL = 0.8 g/kg BW QD	At 0.23 g/kg BW degeneration of the testis tubules, degenerated sperm; from 7 g/kg BW decreased BW gain; at 19 g/kg BW kidney damage; 5♂	Smyth et al[256]
	PO (drinking water)	2 years	0.00085, 0.0036, 0.017, 0.062 g/kg BW QD	NOAEL = 0.062 g/kg BW QD	8♂/8♀	Smyth et al[255]; Smyth et al[242]

Abbreviations: BW, body weight; IP, intraperitoneal; IV, intravenous; LD_{50}, lethal dose for 50% of population; NOAEL, no observed adverse effect level; PEG, polyethylene glycol; PO, oral; QD, once a day.

Table 82. PEG 6,000.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rabbit	IV	Acute	>10 g/kg BW	LD_{50}		Smyth et al[242]
Rat	IP	Acute	6.8 g/kg BW	LD_{50}		Smyth et al[242]
	PO (dietary)	90 days	20, 40, 80, 160, 240 g/kg diet QD (1.5, 3, 6, 12, 18 g/kg BW QD)	NOAEL = 12 g/kg BW QD	At 18 g/kg BW kidney weights increased, decreased BW gain; 5♂/5♀	Smyth et al[243]

Abbreviations: BW, body weight; IP, intraperitoneal; IV, intravenous; LD_{50}, lethal dose for 50% of population; NOAEL, no observed adverse effect level; PEG, polyethylene glycol; PO, oral; QD, once a day.

Table 83. PEG 10,000.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	IP	Acute	12.6 g/kg BW	LD_{50}		Smyth et al[242]
	PO (dietary)	90 days	1.6 g/kg BW QD	NOAEL		Smyth et al[242]

Abbreviations: BW, body weight; IP, intraperitoneal; LD_{50}, lethal dose for 50% of population; NOAEL, no observed adverse effect level; PEG, polyethylene glycol; PO, oral; QD, once a day.

Table 84. PEG 4,000,000.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	IV	Acute	>10 g/kg BW	LD_{50}		Smyth et al[242]
	PO (dietary)	90 days	8.0, 18.4 g/kg BW QD	From 8 g/kg BW cloudy swelling in the renal tubules; at 18.4 g/kg BW decreased BW gain (males), decreased relative liver weights	10♂/10♀	Smyth et al[257]
	PO (dietary)	2 years	Up to 2.76 g/kg BW QD	NOAEL = 2.76 g/kg BW QD	36♂/36♀	Smyth et al[257]
	PO (dietary)	2 years	Up to 0.56 g/kg BW QD	NOAEL = 0.56 g/kg BW QD	4♂/2♀	Smyth et al[257]

Abbreviations: BW, body weight; IV, intravenous; LD_{50}, lethal dose for 50% of population; NOAEL, no observed adverse effect level; PEG, polyethylene glycol; PO, oral; QD, once a day.

Table 85. Petrolatum.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rabbit	Dermal	1 month	1 g/kg	Well tolerated		Gad et al[2]

Table 86. Phosphate-Buffered Saline.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	IV (slow bolus)	28 days	2.5 mL/kg/dose (5 mL/kg/d) BID	Well tolerated	pH 7.2; age 5-6 months; ♂/♀	New contributed data
	1-hour infusion	1-hour infusion single dose	10 mL/kg	Well tolerated	M PBS (powder) in sterile water for injection; beagle dog; age 5 months; ♂/♀	New contributed data
	PO (gavage)	28 days	5 mL/kg QD	Well tolerated	pH 7.2; age 5-6 months; ♂/♀	New contributed data
	Topical	q7d ×2 doses for 7 weeks	1.4 mL/kg divided into 3 doses 60 minutes apart	Well tolerated	Non-GLP; age 7 weeks; 2♂/2♀	New contributed data
Minipig	IV	14 days	5 mL/kg QD	Well tolerated	GLP; pH 6.0; age 17-21 days; 5♂/5♀	New contributed data
	IV	14 days	1 mL/kg QD	Well tolerated	GLP; pH 6.0; age 5-8 months; 5♂/5♀	New contributed data
	PO	7 days	5 mL/kg BID	Well tolerated	GLP; age 4 days; 4♂/4♀	New contributed data
	PO	28 days	5 mL/kg BID	Well tolerated	GLP; pH 6.0; age 4-5 days; 10♂/10♀	New contributed data
Mouse	SC (infusion)	Continuous (24 h/d) infusion for 7 days	1.0 mL/h (+0.15 mL/h)	Well tolerated	pH 7.2; age 10 weeks; ♂/♀	New contributed data
	SC (bolus)	Every 2 days for 1 week and then weekly for 26 weeks	10-11.83 mL/kg	Well tolerated	pH 7.2; age 6 weeks; ♂/♀	New contributed data
	SC	6 months	10 mL/kg	Well tolerated		Gad et al[2]

(continued)

Table 86. (continued)

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Nonhuman primate	IV (slow bolus)	28 days	10 mL/kg QD	Well tolerated	pH 7.2; age 2-3 years; ♂/♀	New contributed data
	PO (gavage)	2 weeks	10 mL/kg/dose	Well tolerated		Gad et al[2]
	PO (gavage)	2 weeks	1.6 mL/kg	Well tolerated		Gad et al[2]
	SC	1 week	0.2 mL/kg	Well tolerated		Gad et al[2]
	SC	9 months	1 mL/kg	Well tolerated		Gad et al[2]
Rabbit	IV	12 weeks	1.0 mL/kg q7d	Well tolerated	Non-GLP; pH 6.5; age 7-8 months; 9♂	New contributed data
Rat	IV	Single dose	1 mL/kg	Well tolerated		Gad et al[2]
	IV (slow bolus)	28 days	5 mL/kg once weekly	Well tolerated	pH 7.2; age 6 weeks; ♂/♀	New contributed data
	PO (gavage)	5 doses	10 mL/kg	Well tolerated		Contributed data, 2006
	PO	28 doses	10 mL/kg	Well tolerated		Gad et al[2]
	PO (gavage)	28 days	10 mL/kg/dose QD	Well tolerated	pH 7.2; age 6 weeks; ♂/♀	New contributed data
	SC	1 month	1 mL/kg QD	Well tolerated		Gad et al[2]
	Slow bolus injection	11 doses	1 mL/kg	Well tolerated		Gad et al[2]

Abbreviations: BID, twice a day; GLP, good laboratory practice; IV, intravenous; PO, oral; QD, once a day; q7d, every 7 days; SC, subcutaneous.

Table 87. Poloxamer 188.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	SC	4 weeks	5 mL/kg QD	Dog vehicle changed following a single administration due to animal distress in response to the injections. The distress was attributed to the vehicle	2% in DI water; pH 5 $\pm$ 0.2; age 5-6 months; ♂/♀	New contributed data
Mouse	PO	1 month	10 mL/kg	Well tolerated	5% solution	Gad et al[2]
Rat	PO	1 month	10 mL/kg	Well tolerated	7.5% Solution	Gad et al[2]
	SC	4 weeks	5 mL/kg QD	None	2% in DI water; pH 5 + 0.2; age 6 weeks; ♂/♀	New contributed data

Abbreviations: DI, deionized; PO, oral; SC, subcutaneous.

Table 88. Poly(glycolide-co-dl-lactide) Microspheres.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	Into periodontal pockets	28 days	3.5 mg/pocket SD	Well tolerated	GLP; age 6-10 years	New contributed data

Abbreviations: GLP, good laboratory practice; SD, single dose.

Table 89. Polyglycerol Oleate.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rabbit	Dermal	Acute		Moderately irritant (irritation and corrosion test)	No dilution	Gattefossé Technical Document[349]
	Ocular	Acute		Slightly irritant (irritation and corrosion test)	No dilution	Gattefossé Technical Document[349]
Rat	PO	Acute		$LD_{50} \geq$ 2,005 mg/kg/d	No dilution	Gattefossé Technical Document[349]

Abbreviations: LD_{50}, lethal dose for 50% of population; PO, oral.

Table 90. Polyvinylpyrrolidone.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO	Acute		Causes histamine release in dogs. The reaction is highly variable ranging from no discernible effect, to reddening of extremities, to total collapse		New contributed data
Rat	IM	Single dose	1 mL	Well tolerated	1%	Gad et al[2]

Abbreviations: IM, intramuscular; PO, oral.

Table 91. Propylene Glycol.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	IV	Single dose	1 mL/kg	NOAEL; some emesis and diarrhea	30%	New contributed data
	IV	14 days	5 mL/kg at a rate of 0.3 mL/kg	Hemolysis in vitro dog blood	60% solution in water	New contributed data
	IV (bolus)		1 mL/kg	Well tolerated	40% solution in water pH 3-11; 50% PG causes hemolysis	Strickley[8]
	IV (infusion)		2 mL/kg	Well tolerated	40% solution in water pH 3-11; 50% PG causes hemolysis	Strickley[8]
	PO	28 days	1.5 mL/kg	Well tolerated	100%	New contributed data
	PO	1 month	2.5 mL/kg	Well tolerated		Gad et al[2]
	PO (gavage)	Up to 7 days	2 mL/kg/d	Well tolerated		Gad et al[2]
	PO (gavage)	90 days	Dose volume 5 mL/kg, daily dose 1,000 mg/kg (20% wt/vol)	Well tolerated	Dose concentration 200 mg/mL	Thackaberry[155]
Minipig	Dermal	26 weeks	2.5 mL/kg	Well tolerated		Gad et al[2]
Nonhuman primate	PO (gavage)	90 days	Dose volume 5 mL/kg, daily dose 1,000 mg/kg (20% wt/vol)	Well tolerated	Dose concentration 200 mg/mL	Thackaberry[155]
Mouse	IP	1 month	2.5 mL/kg	Well tolerated	40% solution	Gad et al[2]
	IV	Range finding	MTD: 1.5 g/kg; NOEL: 1 g/kg		Published $LD_{50} = 5.0$-8.6 g/kg	Sambrone[6]
	IV (into tail vein)	Acute	1,036 mg/kg (dose volume 5 mL/kg)	NOEL	20% solution	Thackaberry[252]
	IV (into tail vein)	Acute	1,554 mg/kg (dose volume 5 mL/kg)	MTD; tremors and hind limb ataxia; full recovery by 1 min is typical	30% solution	Thackaberry[252]
	PO	1 month	10 mL/kg	Well tolerated	50% solution	Gad et al[2]
	PO (gavage)	90 days	Dose volume 10 mL/kg, daily dose 1,000 mg/kg (20% wt/vol)	Well tolerated	Dose concentration 100 mg/mL	Thackaberry[155]
Rat	IV (bolus)		2 mL/kg	Well tolerated	40% solution in water pH 3-11; 50% PG causes hemolysis	Strickley[8]
	IV (infusion)		5 mL/kg	Well tolerated	40% solution in water pH 3-11; 50% PG causes hemolysis	Strickley[8]
	PO	1 month	2.5 mL/kg	Well tolerated		Gad et al[2]
	PO (gavage)	Prelim/ segment II	5 mL/kg/d	Well tolerated	60/40: purified water/ propylene glycol: wt/wt	Contributed data, 2006
	PO (gavage)	2 weeks	5 mL/kg/d	Well tolerated	60/40: purified water/ propylene glycol: wt/wt	Contributed data, 2006
	PO (gavage)	Segment II	5 mL/kg/d	Well tolerated	60/40: purified water/ propylene glycol: wt/wt	Contributed data, 2006
	PO (gavage)	2 weeks	2 mL/kg/d	Well tolerated		Gad et al[2]
	PO (gavage)	90 days	Dose volume 5 mL/kg, daily dose 1,000 mg/kg (20% wt/vol)	Well tolerated	Dose concentration 200 mg/mL	Thackaberry[155]
	SC	4 weeks	2.5 mL/kg/d	Well tolerated		Gad et al[2]

Abbreviations: IP, intraperitoneal; IV, intravenous; LD_{50}, lethal dose for 50% of population; MTD, maximum tolerated dose; NOEL, no adverse effect level; PG, propylene glycol; PO, oral; SC, subcutaneous.

Table 92. Randomly Methylated β-Cyclodextrins.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Nonhuman primate	Intranasal	1 month	82.8 mg/mL (with treatment), 74.7 mg/mL (placebo) TID	Well tolerated	7.5%	Gad et al[2]

Abbreviation: TID, 3 times a day.

Table 93. Safflower Oil.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	SC	Single dose	1 mL	Well tolerated; no evidence of irritation macroscopically or histologically	100%	New contributed data

Abbreviation: SC, subcutaneous.

Table 94. Saline (pH Adjusted).

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Mouse	IM	14 days	4 mL/kg SD	None	(pH 4.5); non-GLP; age 6 weeks; 8♂/8♀	New contributed data

Abbreviations: GLP, good laboratory practice; IM, intramuscular; SD, single dose.

Table 95. Sesame Oil.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO	1 month	5 mL/kg	Well tolerated		Gad et al[2]
	PO (gavage)	28 days	5 mL/kg QD	None	Age 7-8 months; ♂/♀	New contributed data
	PO (gavage)	9 months	1 mL/kg QD	None	Age 7-8 months; ♂/♀	New contributed data
Mouse	PO	1 month	0.25 mL/kg	Well tolerated		Gad et al[2]
Rabbit	PO	1 month	0.5 mL/kg	Well tolerated		Gad et al[2]
Rat	PO	1 month	1 mL/kg	Well tolerated		Gad et al[2]
	PO (gavage)	26 weeks	1 mL/kg QD	None	Age 6 weeks; ♂/♀	New contributed data

Abbreviations: PO, oral; QD, once a day.

Table 96. Sodium Acetate Trihydrate Buffer.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Nonhuman primate	IV		1 mL/kg	Well tolerated		Gad et al[2]

Abbreviation: IV, intravenous.

Table 97. Sodium Chloride.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Cat	SC	9 days	0.1 mL/kg QD	None	0.9% saline; non-GLP; age 4 months; 2♂/2♀	New contributed data
	SC	9 days	0.1 mL/kg QD	None	Non-GLP; 2♂/2♀	New contributed data
	IV	8 days	1.9 mL/kg SD	None	0.9% saline; non-GLP; age 8-9 months; 2♂/2♀	New contributed data
	IV	19 days	1.32 mL/kg 3×/wk × 2 weeks	None	0.9% saline; non-GLP; age 8-9 months; 2♂/2♀	New contributed data

(continued)

Table 97. (continued)

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	IV	Single dose	10 mL/kg	Well tolerated	0.9%	Gad et al[2]
	IV	Single dose	2 mL/kg	Well tolerated	0.9%	Gad et al[2]
	IV	2 weeks	5 mL/kg/d	Well tolerated	0.9%	Gad et al[2]
	IV (bolus)	Single dose	0.3 mL/kg	Well tolerated	0.9%	Gad et al[2]
	IV	14 days	2.5 mL/kg QD	None	0.9% saline and water to make 0.8% saline; GLP; age 8 weeks; 10♂/10♀	New contributed data
	IV	14 days	2 mL/kg QD	None	0.9% saline and water to make 0.8% saline; GLP; age 10-11 months; 12♂/12♀	New contributed data
	IV (infusion)	8 weeks	1 mL/kg 30-minute infusion 3×/wk	None	Non-GLP; age 8-15 months; 2♀	New contributed data
	IV (infusion)	48 hours	2 mL/kg 20-minute infusion SD	None	0.9% saline; non-GLP; age 8-13 months; 2♂/2♀	New contributed data
	IV (infusion)	4 hours	2 mL/kg 20-minute infusion SD	None	0.9% saline; non-GLP; age 8-9 months; 1♀	New contributed data
	Ocular	6 months	1 drop/eye TID	None	0.9% saline; GLP; age 6-7 months; 4♂/4♀	New contributed data
	PO	Single dose	0.282 mL/kg	Well tolerated	0.9%	Gad et al[2]
	SC	1 month	0.025 mL	NOEL	0.9%	Gad et al[2]
	SC	6 months	0.5 mL/kg total; 0.1 mL/kg at 5 separate locations q21d	Occasional transient injection site erythema	0.9% saline; GLP; age 5-6 months; 4♂/4♀	New contributed data
Minipig	SC	28 days	0.0225 mL/kg QD	None	0.9% saline; GLP; age 3 months; 4♂/4♀	New contributed data
	IM	49 days	0.5 mL q28d × 2 doses	None	0.9% saline; non-GLP; age 4 months; 3♂	New contributed data
	ID	49 days	0.5 mL q28d × 2 doses	None	0.9% saline; non-GLP; age 4 months; 3♂	New contributed data
Mouse	IM	30 doses		Well tolerated	0.9%	Contributed data, 2006
	IV	Single dose	10 mL/kg	Well tolerated	0.9%	Gad et al[2]
	IV	2 days	10 mL/kg SD	None	0.9% saline and water to make 0.8% saline; GLP; age 4-7 weeks; 11♂/11♀	New contributed data
	SC	Single dose	10 mL/kg	Well tolerated	0.9%	Gad et al[2]
	Topical	7 days	0.10 mL QD	None	0.9% saline; non-GLP; age 8 weeks; 28♂	New contributed data
Nonhuman primate	SC	28 doses	0.67 mL/kg	Well tolerated	0.9%	Gad et al[2]
	SC	56 doses	0.5 mL/kg/dose	Well tolerated	0.9%	Gad et al[2]
	Slow bolus	9 doses	10 mL/kg/dose	None	0.9%	Contributed data, 2006
Rabbit	IM	33 days	0.2 mL q14d × 3 doses	None	0.9% saline; GLP; age 6 months; 6♀	New contributed data
	IV	Single dose	0.1 mL/kg	Well tolerated	0.9%	Gad et al[2]
	Perivascular	Single dose	0.1 mL/kg	Well tolerated	0.9%	Contributed data, 2006
	SC	Single dose	0.5 mL/kg	Well tolerated	0.9%	Contributed data, 2006

(continued)

Table 97. (continued)

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	IP	90 days	10 mL/kg QD	None	0.9% saline; GLP; age 9 weeks; 10♂/10♀	New contributed data
	IV	6 hours	4 μL/g SD	None	0.9% saline; non-GLP; age 8-9 weeks; 2♂/2♀	New contributed data
	IV	Single dose	1 mL/kg	Well tolerated	0.9%	Gad et al[2]
	IV	Single dose	2 mL/kg	None	0.9%	Contributed data, 2006
	IV	Single dose	10 mL/kg	Well tolerated	0.9%	Contributed data, 2006
	IV	3 doses	4 mL/kg	Well tolerated	0.9%	Gad et al[2]
	IV	3 days	0.376 mL/kg QD	None	0.9% saline; GLP; age 4 months; 5♂	New contributed data
	IV	7 doses	1 mL/kg	None	0.9%	Contributed data, 2006
	IV	2 weeks	10 mL/kg/d	Well tolerated	0.9%	Gad et al[2]
	IV infusion	13 weeks	10 mL/kg 30-minure infusion q7d	None	0.9% saline; GLP; age 11 weeks; 20♂/20♀	New contributed data
	SC	Single dose	0.1-0.4 mL	Well tolerated	0.9%	Contributed data, 2006
	SC	14 days	0.5 mL/kg QD	None	0.9% saline; GLP; age 71-72 days; 15♂/15♀	New contributed data
	SC	28 doses	4 mL/kg	Well tolerated	0.9%	Gad et al[2]
	SC	56 doses	2 mL/kg/dose	Well tolerated	0.9%	Gad et al[2]
	Slow bolus	Single dose	1 mL/kg	Well tolerated	0.9%	Gad et al[2]
	Slow bolus	Single dose	5 mL/kg	Well tolerated	0.9%	Contributed data, 2006
	Slow bolus	Single dose	10 mL/kg	Well tolerated	0.9%	Gad et al[2]
	Slow bolus	3 doses	2 mL/dose	Well tolerated	0.9%	Contributed data, 2006

Abbreviations: GLP, good laboratory practice; ID, intradermal; IM, intramuscular; IV, intravenous; NOEL, no adverse effect level; PO, oral; QD, once a day; q7d, every 7 days; q14d, every 14 days; q21d, every 21 days; q28d, every 28 days; SC, subcutaneous; SD, single dose; TID, 3 times a day.

Table 98. Sodium Dihydrogen Phosphate Dihydrate.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Mouse	PO (gavage)	91 days	10 mL/kg QD	None	0.5 mol/L SDPD in DI water; age 5 weeks; ♂/♀	New contributed data
Nonhuman primate	PO (gavage)	91 days	10 mL/kg QD	None	0.5 mol/L SDPD in DI water; age 2.5-3.5 years; ♂/♀	New contributed data

Abbreviations: DI, deionized; PO, oral; SDPD, sodium dihydrogen phosphate dehydrate; QD, once a day.

Table 99. Sodium Metabisulfite.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Mouse	PO (gavage)	91 days	20 mL/kg QD	Well tolerated	10% in distilled water; age 6 weeks; ♂/♀	New contributed data
Nonhuman primate	PO (gavage)	91 days	10 mL/kg QD	Well tolerated	10% in distilled water; age 2-4.5 years; ♂/♀	New contributed data
Rat	PO (gavage)	91 days	10 mL/kg QD	Well tolerated	10% in distilled water; age 6 weeks; ♂/♀	New contributed data

Abbreviations: PO, oral; QD, once a day.

Table 100. Sodium Phosphate Buffer.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO	14 doses	10 mL/kg/dose	Well tolerated	70 mmol/L	Gad et al[2]
Mouse	PO (gavage)	90 days	10 mL/kg QD	Well tolerated	0.1 mol/L; pH 7.0; age 6 weeks; ♂/♀	New contributed data
Nonhuman primate	PO (gavage)	90 days	5 mL/kg QD	Well tolerated	0.1 mol/L; pH 7.0; age 2-3 years; ♂/♀	New contributed data
	PO (gavage)	91 days	5 mL/kg QD	Well tolerated	0.1 mol/L; pH 7.0; age 2-3 years; ♂/♀	New contributed data
Rat	PO	2 weeks	10 mL/kg QD	Well tolerated	70 mmol/L	Gad et al[2]
	PO (gavage)	90 days	10 mL/kg QD	None	0.1 mol/L; pH 7.0; age 6 weeks; ♂/♀	New contributed data
	PO (gavage)	91 days	10 mL/kg QD	None	0.1 mol/L; pH 7.0; age 6 weeks; ♂/♀	New contributed data

Abbreviations: PO, oral; QD, once a day.

Table 101. Sodium Sulfite.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rabbit	Ocular (topical)	28 days	50 mL/dose QID	None	10% in reverse osmosis DI water; age 7 months; ♂/♀	New contributed data

Abbreviations: DI, deionized; QID, 4 times a day.

Table 102. Solutol HS15.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	Any	1 dose	Varies	Poorly tolerated in significant amounts	Solutol HS15/purified water	New contributed data
Mouse	IP	2 weeks	10 mL/kg 3×/wk	None	10% Solutol; non-GLP; age 4-5 weeks; 5♂/5♀	New contributed data
	IV	2 weeks	10 mL/kg 3×/wk	None	10% Solutol; non-GLP; age 4-5 weeks; 5♂/5♀	New contributed data
Rat	PO (gavage)	2 months	10 mL/kg/d	Well tolerated	10% Solutol HS15 in purified water; Sprague Dawley rats	Contributed data, 2006

Abbreviations: GLP, good laboratory practice; IP, intraperitoneal; IV, intravenous; PO, oral.

Table 103. Soybean Oil.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO	Acute		Well tolerated	50%	Cambridge MedChem Consulting[310]
Rat	PO	13 weeks	2,000 mg/kg	Well tolerated; reduced food consumption at 500 mg/kg and above		Kawashima et al[313]
	PO	13 weeks	20% in diet	Well tolerated		Earl et al[312]

Abbreviation: PO, oral.

Table 104. Sulfobutylether-β-cyclodextrin.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Mouse	PO	7 days	10 mL/kg BID	None	10%; non-GLP; age 7 weeks; 3♂/3♀	New contributed data

Abbreviations: BID, twice a day; GLP, good laboratory practice; PO, oral.

Table 105. Tartaric Acid.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rabbit	PO (gavage)	Prelim segment II	3 mL/kg/d	Well tolerated		Gad et al[2]
	PO (gavage)	Segment II	3 mL/kg/d	Well tolerated		Gad et al[2]
Rat	PO (gavage)	39 weeks	0.5 mL/kg	Well tolerated		Gad et al[2]
	PO (gavage)	Single dose	3 mL/kg	Well tolerated		Gad et al[2]

Abbreviation: PO, oral.

Table 106. Terbinafine HCl Placebo Nail Lacquer.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Pig	Dermal	1 month	600 μL/kg	Erythema, peeling, or flaking skin		Contributed data, 2006

Table 107. Transcutol.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Cat	IV	1 month	2 mL/kg, single dose	Well tolerated	No evidence of hemolysis or hematotoxicity	Gad et al[2]
	IV	Acute	1,000 mg/kg	LD_{50}		Sullivan et al[328]
Dog	IV	Acute	3,000 mg/kg	LD_{50}		Sullivan et al[328]
	PO	90 days	1,500 mg/kg/d	NOAEL		Sullivan et al[328]
	PO (gavage)	Acute (dose escalating)	500, 1,000, 1,500, 2,000 mg/kg	MTD > 2,000 mg/kg	Undiluted	Sullivan et al[328]
	PO (gavage)	Subacute (7-day DRF)	0, 500, 1,000, 2,000 mg/kg/d	MTD > 2,000 mg/kg/d		Sullivan et al[328]
	PO (gavage)	Subchronic (13 weeks)	0, 400, 1,000, 2,000/1,500 mg/kg/d	NOAEL = 1,000 mg/kg/d		Sullivan et al[238]
Guinea pig	PO	Acute	300 mg/kg	LD_{50}		Sullivan et al[328]
Minipig	PO	90 days	0, 167, 500, 1,500 mg/kg/d	NOAEL = 167 mg/kg/d	Uremea, death at 1,500 mg/kg/d; high dose reduced to 1,000 mg/kg/d after 21 days; histopath in doses >500 mg/kg/d includes hydropic degeneration of liver and proximal kidney tubules; at >1,000 mg/kg/d increased relative kidney weight and decreased RBC (males)	Sullivan et al[328]
Mouse	IP	Acute	3,900 mg/kg	LD_{50}		Sullivan et al[328]
	IV	Acute	4,300 mg/kg	LD_{50}		Sullivan et al[328]
	IV (bolus, tail vein)	Acute (dose escalating)	25, 50, 100, 200, 400, 800, 1,600, 6,400, 3,200, and 4,800 mg/kg	MTD (IV): 3,200 mg/kg	Males; physiological saline solution	Sullivan et al[328]
	IV (bolus, tail vein)	Acute (dose escalating)	25, 50, 100, 200, 400, 800, 1,600, 8,000, 6,400, 4,800, and 3,200 mg/kg	MTD (IV): 3,200 mg/kg	Females; physiological saline solution	Sullivan et al[328]
	PO	Acute	6.6 g/kg	Tested toxic		Sullivan et al[328]
	PO	Acute	7,250 mg/kg	LD_{50}		Sullivan et al[328]
	PO (gavage)	Developmental (dosed GD 7-14, littered and reared to PND 3)	5,500 mg/kg/d	No developmental toxicity	>99% pure; 50 mated CD1 mice; 14% maternal mortality, maternal weight gain decreased, and no external malformations on pups	Sullivan et al[328]
	PO	90 days	300, 900, 2,700, and 8,100 mg/kg BW (0%, 0.2%, 0.6%, 1.8%, 5.4% in diet, respectively)	NOAEL = 850-1,000 mg/kg BW (0.6% in diet)	At 8,100 mg/kg BW intracellular edema of the kidney, increased organ weights, decreased RBC (males), liver cell enlargement, protein inclusions in bladder lumen (males), tubular degeneration, and atrophy; at 2,700 mg/kg BW, increased relative kidney weights in males was seen	Sullivan et al[328]
	PO	Chronic (12 months)	850-1,000 mg/kg	NOEL		Sullivan et al[328]

(continued)

Table 107. (continued)

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
	SC	Acute	5,500 mg/kg	LD_{50}		Sullivan et al[328]
Rabbit	Dermal	Skin irritation	0.5 mL over 2 cm^2 area	Nonirritant	50%	Gad et al[2]
	Dermal	28 days	0, 300, 1,000, 3,000 mg/kg/d	NOEL > 1,000 mg/kg/d	Undiluted	Gad et al[2]
	IM	14 days	0, 0.62, 0.82, 1.6 mL/kg/d	NOAEL = 1.6 mL/kg/d	No treatment-related effects	Sullivan et al[328]
	Ocular	Eye irritation	0.1 mL	Slight irritation	30%	Gad et al[2]
	Ocular	Eye irritation	0.1 mL	Slight irritation	Undiluted	Gad et al[2]
	PO	Acute	3,620 mg/kg	LD_{50}		Sullivan et al[328]
	SC	Acute	2,000 mg/kg	LD_{50}		Sullivan et al[328]
Rat	Inhalation (nasal)	28 days (6 h/d, 5 d/wk)	0, 16, 49, 200 ppm (0, 90, 270, 1,100 mg/m3, respectively)	NOAEL = 1,100 mg/m^3	No systemic effects; mild local irritation; focal necrosis in larynx (males); 1,100 mg/m^3 was higher than maximum concentration at which only vapor present	Sullivan et al[328]
	Inhalation (whole body)	Developmental (7 h/d from GD 7-15)	0, 102 ppm	No maternal or fetal toxicity	98%-99.5% pure; Sprague Dawley rats	Sullivan et al[328]
	IP	Acute	6,300 mg/kg	LD_{50}		Sullivan et al[328]
	IV	Acute	4,000 mg/kg	LD_{50}		Sullivan et al[328]
	PO	Acute	7,500 mg/kg	LD_{50}		Sullivan et al[328]
	PO	Acute	5.0 g/kg	LD_{50} > 5,000 mg/kg	Undiluted	Gad et al[2]
	PO	90 days	0%, 0.25%, 1%, and 5%	NOEL = 1%		Gad et al[2]
	PO (gavage)	90 days	250, 2,500 mg/kg BW (0.5% and 5.0% in diet, respectively)	NOAEL = 250 mg/kg BW	High-dose group saw reduction in growth rate and food consumption, decreased hemoglobin, decreased RBC (females), oxalate crystals in urine (females), increased organ weights, calcification of renal cortex; CFE rats	Sullivan et al[328]
	PO (gavage)	Fertility (segment I)	0, 300, 1,000, 2,000 mg/kg/d	NOAEL (oral) = 2,000 mg/kg/d	In sterile water	Sullivan et al[328]
	PO (gavage)	6 weeks	1,340, 2,680, 5,360 mg/kg/d	NOAEL = 1,340 mg/kg/d	Death, hematological/clinical signs in intermediate- and high-dose groups; lethargy during first week; 10♂; Sprague Dawley rats	Sullivan et al[328]
	PO (gavage)	Embryo/fetal development study (segment II)	0, 300, 1,000, 2,000 mg/kg/d	NOAEL (DevTox, MatTox) 1,000 mg/kg/d	In sterile water	Sullivan et al[328]
	PO	Fertility and embryotoxicity range finding study	500, 1,000, 2,000, 4,000 mg/kg/d	NOEL > 500 mg/kg/d		Gad et al[2]
	SC	Acute	6,000 mg/kg	LD_{50}		Sullivan et al[328]

Abbreviations: BW, body weight; DRF, dose range finding; GD, gestation day; IM, intramuscular; IP, intraperitoneal; IV, intravenous; LD_{50}, lethal dose for 50% of population; MTD, maximum tolerated dose; NOAEL, no observed adverse effect level; PND, postnatal day; PO, oral; RBC, red blood cell; SC, subcutaneous.

Table 108. Trisodium Citrate Dihydrate.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO (gavage)	52 weeks	10 mL/kg/d	Well tolerated	2.65% aqueous (pH 6.4)	Gad et al[2]
Hamster	PO (gavage)	13 weeks	10 mL/kg/d	Well tolerated	2.65% aqueous (pH 6.4)	Contributed data, 2006
Mouse	PO (gavage)	13 weeks	10 mL/kg/d	Well tolerated	2.65% aqueous (pH 6.4)	Gad et al[2]
Rat	PO (gavage)	4 weeks	10 mL/kg/d	Well tolerated	2.65% aqueous (pH 6.4)	Gad et al[2]
	PO (gavage)	Segment III	10 mL/kg/d	Well tolerated	2.65% aqueous (pH 6.4)	Gad et al[2]
	PO (gavage)	39 weeks	10 mL/kg/d	Well tolerated	2.65% aqueous (pH 6.4)	Gad et al[2]

Abbreviation: PO, oral.

Table 109. Tween 20.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	IV, SC, IP	Single dose		Not tolerated in any significant amount		New contributed data
	PO	Single dose		Poorly tolerated in significant amounts		New contributed data
Mouse	PO	Acute	10 g/kg	Well tolerated		Contributed data, 2006
	PO		10 g/kg	Well tolerated		Gad et al[2]
Nonhuman primate	IV (slow bolus)	28 days	10 mL/kg 3×/wk	Red/back discoloration of the skin (anogenital region and hindlimbs and forelimbs)	1.01% in sterile water for injection, USP; age 2-3 years; ♂/♀	New contributed data
Rat	PO	1 month	250 mg/kg	Well tolerated		Gad et al[2]
	PO	90 days	500 g/kg	Diarrhea		Gad et al[2]
	IV (slow bolus)	6 months	10 mL/kg 3×/wk	None	1.01% in sterile water for injection, USP; age 7-8 weeks; ♂/♀	New contributed data

Abbreviations: IP, intraperitoneal; IV, intravenous; PO, oral; SC, subcutaneous; USP, United States Pharmacopeia.

Table 110. Tween 80.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	IV, SC, IP	Single dose	Varies	Not tolerated in any significant amount; hypersensitivity		New contributed data; Thackaberry et al[155]
	PO	Single dose	Varies	Poorly tolerated in significant amounts		New contributed data
	PO (gavage)	ADME	5 mL/kg/d	Well tolerated	0.1%	Gad et al[2]
	PO (gavage)	90 days	Dose volume 5 mL/kg, daily dose 10 mg/kg (0.2% wt/vol)	Well tolerated	Dose concentration 2 mg/mL	Thackaberry et al[155]
Mouse	Intranasal	3 days	10 μL/nostril	Well tolerated	0.2%	Gad et al[2]
	IP	1 month	10 mL/kg	Well tolerated	2% solution	Gad et al[2]
	PO (gavage)	35 days	10 mL/kg BID	Distended abdomen, skin cold to the touch, feces few/absent, limb function impaired, head tilt, swollen abdomen, death; vehicle was not tolerated following 35 days of daily administration	10% in distilled water; age 6 weeks; ♂/♀	New contributed data
	PO (gavage)	90 days	Dose volume 10 mL/kg, daily dose 10 mg/kg (0.2% wt/vol)	Well tolerated	Dose concentration 1 mg/mL	Thackaberry et al[155]
Nonhuman primate	PO (gavage)	Efficacy	5 mL/kg/d	Well tolerated	0.1%	Gad et al[2]
	PO (gavage)	90 days	Dose volume 5 mL/kg, daily dose 10 mg/kg (0.2% wt/vol)	Well tolerated	Dose concentration 2 mg/mL	Thackaberry et al[155]

(continued)

Table 110. (continued)

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	IP	Efficacy	10 mL/kg/d	Well tolerated	0.2%	Contributed data, 2006
	IV	Acute	100 mg/kg	Well tolerated		Gad et al[2]
	PO	Acute	350 mg/kg	Well tolerated		Gad et al[2]
	PO	7 days	10 mL/kg	Well tolerated	1% solution	Gad et al[2]
	PO (dietary)		2% (1 g/kg)	NOAEL		Thackaberry et al[155]
	PO (gavage)	4 weeks	5 mL/kg/d	Well tolerated	0.1%	Gad et al[2]
	PO (gavage)	90 days	Dose volume 5 mL/kg, daily dose 10 mg/kg (0.2% wt/vol)	Well tolerated	Dose concentration 2 mg/mL	Thackaberry et al[155]

Abbreviations: ADME, absorption, distribution, metabolism, excretion; BID, twice a day; IP, intraperitoneal; IV, intravenous; NOAEL, no observed adverse effect level; PO, oral; SC, subcutaneous.

Table 111. Vitamin E TPGS.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO (gavage)	32 days	5 mL/kg QD	None	20% in DI water; age 5-5.5 months; ♂/♀	New contributed data
Rat	PO (gavage)	QD for 4 days, then off for 4 days (×5 cycles) for a total of 32 days	10 mL/kg	None	20% in DI water; age 6 weeks; ♂/♀	New contributed data
	PO (gavage)	Single dose	10 mL/kg	None	10% vitamin E TPGS in DI water; age 6 weeks; ♂	New contributed data

Abbreviations: DI, deionized; PO, oral; QD, once a day; TPGS, D-α-tocopheryl polyethylene glycol succinate.

Table 112. Water.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Dog	PO (gavage)	14 doses	10 mL/kg/dose	None	Distilled	Contributed data, 2006
	PO (gavage)	28 doses	5 mL/kg/d	None	Distilled	Contributed data, 2006
	PO (gavage)	30 doses	10 mL/kg	None	Distilled	Contributed data, 2006
	PO	9 months	0.052 mL/kg TID	None	GLP; age 5-6 months; 6♂/6♀	New contributed data
Minipig	SC and IA	q7d 3× weeks for 90 days	12 mL total; 2 mL/site	None	GLP; age 5-6 months; 4♂/4♀	New contributed data
Mouse	PO (gavage)	2 doses	20 mL/kg/d	None	Distilled	Contributed data, 2006
	PO (gavage)	28 doses	10 mL/kg	None	Deionized	Contributed data, 2006
Nonhuman primate	PO (gavage)	14 doses	10 mL/kg	None	Sterile, USP	Contributed data, 2006
	PO (gavage)	28 doses	10 mL/kg	None	Deionized	Contributed data, 2006
Pig	Dermal	9 doses	10 mL/animal/d	None	Deionized	Contributed data, 2006

(continued)

Table 112. (continued)

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Rat	IV	11 doses	5 mL/kg	None	Sterile, USP	Contributed data, 2006
	IV (slow bolus)	4 doses	4 mL/kg	None	Sterile, USP	Contributed data, 2006
	PO (gavage)	Single dose	5 mL/kg	None	Sterile, USP	Contributed data, 2006
	PO (gavage)	Single dose	5 mL/kg	None	Deionized	Contributed data, 2006
	PO (gavage)	Single dose	10 mL/kg	None	Distilled	Contributed data, 2006
	PO (gavage)	Single dose	10 mL/kg	None	Deionized	Contributed data, 2006
	PO (gavage)	Single dose	10 mL/kg	None	Sterile, USP	Contributed data, 2006
	PO	Single dose	20 mL/kg	None	Sterile, USP	Contributed data, 2006
	PO (gavage)	5 doses	10 mL/kg	None	Deionized	Contributed data, 2006
	PO (gavage)	14 doses	5 mL/kg	None	Sterile, USP	Contributed data, 2006
	PO (gavage)	14 doses	10 mL/kg	None	Distilled	Contributed data, 2006
	PO (gavage)	14 doses	10 mL/kg	None	Sterile, USP	Contributed data, 2006
	PO	26 weeks	5 mL/kg TID	None	GLP; age 6 weeks; 25♂/25♀	New contributed data
	PO (gavage)	28 doses	5 mL/kg	None	Deionized	Contributed data, 2006
	PO (gavage)	28 doses	10 mL/kg	None	Deionized	Contributed data, 2006
	PO (gavage)	30 doses	10 mL/kg	None	Distilled	Contributed data, 2006

Abbreviations: GLP, good laboratory practice; IA, intra-articular; IV, intravenous; PO, oral; q7d, every 7 days; SC, subcutaneous; TID, 3 times a day; USP, United States Pharmacopeia.

Table 113. Xylitol.

Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
Nonhuman primate	Intranasal	1 month	Control and high dose of 1,200 μL/d; intermediate dose of 400 μL/d; low dose of 200 μL/d	Well tolerated at 1,200 μL/d	3.3% in water (wt/vol)	Gad et al[2]

Table 114. Combination Formulations.

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
1	Acacia (10%)/Antifoam 1510-US (0.05%)/water (purified)	Rat	PO (gavage)	14 days	10 mL/kg QD	Well tolerated	Age 9-11 weeks; ♂/♀	New contributed data
2	Acacia gum (10%)/DMSO (1%)	Nonhuman primate	PO (gavage)	2 months (ADME)	5 mL/kg	Well tolerated		Contributed data, 2006
3	Acacia gum (10%)/DMSO (1%)	Rat	PO (gavage)	1 week (ADME)	5 mL/kg	Well tolerated	Sprague Dawley	Contributed data, 2006
4	Acacia gum (10%)/DMSO (1%)	Rat	PO (gavage)	1 month (ADME)	5 mL/kg	Well tolerated	Sprague Dawley	Contributed data, 2006
5	Acacia gum (10%)/DMSO (1%)	Rat	PO (gavage)	1 month (ADME)	5 mL/kg	Well tolerated	Sprague Dawley	Contributed data, 2006
6	Acacia gum (10%)/Tween 80 (0.5%)	Rat	PO (gavage)	Prelim/segment II	5 mL/kg/d	Well tolerated		Contributed data, 2006
7	Acacia gum (10%)/Tween 80 (0.5%)	Rat	PO (gavage)	Segment II	5 mL/kg/d	Well tolerated		Contributed data, 2006
8	Acetate buffer (pH 5)/benzyl alcohol (1% pH 5.0; acetate: 100 mmol/L, citrate: 10 mmol/L)	Nonhuman primate	IV (into saphena vein)	2 weeks	0.92 mL/kg	Well tolerated		Contributed data, 2006
9	Acetate buffer pH 5 with 1.0% benzyl alcohol (acetate: 100 mmol/L, citrate: 10 mmol/L); pH 5.0	Rat	IV (into tail vein)	28 days	0.92 mL/kg	Well tolerated	Sprague Dawley	Contributed data, 2006
10	Acetic acid (0.01 mol/L)/DMA (95/5)	Dog	30-minute infusion	1 day	3 mL/kg in single infusion	None	99% solution; beagles age 5 months; ♂/♀	New contributed data
11	Acetone/cyclohexane (50/50)	Rat	Dermal	6 hours daily, 5 d/wk over 14 days	1.5 mL/kg	None	100% solution; no sham group; age ~60 days; ♀	New contributed data
12	Acetonitrile/acetic acid (99/1)	Dog	PO (dietary)	Ad libitum over 1 year		None	Age 7-8 months; ♂/♀	New contributed data
13	Benzyl alcohol: 60.2%/citric acid: 0.1%/BHT: 0.1%	Cat	Topical	24 hours	0.3 mL SD	None	Non-GLP; age 1 year; 1♂/1♀	New contributed data
14	BHT/benzyl alcohol/isopropanol	Dog	Topical	q7d × 2 doses over 7 weeks	1.4 mL/kg divided into 3 doses 60 minutes apart	None	Non-GLP; age 7 weeks; 4♂/4♀	New contributed data
15	Capmul MCM/Kolliphor EL (50/50)	Nonhuman primate	PO (gavage)	Once weekly over 4 weeks	5 mL/kg	None	Age 3-6 years; ♂/♀	New contributed data
16	Capmul MCM NF/propylene glycol/ Kolliphor EL in a ratio of 1:1:1 (by weight)	Rat	PO	13 weeks	3 mL/kg BID	Well tolerated	Wistar Hans (CRL) age ~7-9 weeks at study initiation; ♂/♀	New contributed data
17	Captisol (5.4%)/dextrose (2.5%)/ water (pH 4)	Dog	IV (infusion)	3 days	2 mL/kg/h, 24 h/d	None	Age 7-8 months; ♂/♀	New contributed data
18	Citrate buffer (50 mmol/L containing 0.5% Methocel E50 Premium LV and 0.2% Tween 20, pH 4 ± 0.1)	Rat	PO (gavage)	14 days	10 mL/kg QD	None	Age 8-9 weeks; ♂/♀	New contributed data
19	Citrate buffer (53.8-54.9 mmol/L containing 0.5% Methocel E50 Premium LV and 0.2% Tween 20, pH 4 ± 0.1)	Nonhuman primate	PO (gavage)	1 day	5 mL/kg SD	None	Age 3-6 years; ♂	New contributed data

(continued)

Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
20	CMC (0.5%)/Tween 80 (0.1% [wt/wt])	Rabbit	PO (gavage)	Prelim/segment III	5 mL/kg/d	Well tolerated		Contributed data, 2006
21	CMC (1%)/Tween 80 (0.5%)	Dog	PO	28 days	10 mL/kg	Well tolerated		Contributed data, 2006
22	CMC (1%)/Tween 80 (0.5%)	Rat	PO	28 days	20 mL/kg	Well tolerated		Contributed data, 2006
23	CMC (high viscosity, 0.25%)/Tween 80 (0.2%)/water (sterile for injection, USP)	Mouse	PO (gavage)	102 weeks	10 mL/kg QD	None	Age 6 weeks; ♂/♀	New contributed data
24	CMC (low viscosity, 1%)/Tween 80 (0.01%)/water (distilled)	Rat	PO (gavage)	105 weeks	10 mL/kg QD	None	Age 6 weeks; ♂/♀	New contributed data
25	CMC (low viscosity, 1%)/Tween 80 (0.01%)/water (distilled)	Nonhuman primate	PO (gavage)	≤365 days	10 mL/kg QD	None	Age 4.5-8 years; ♂/♀	New contributed data
26	CMC (low viscosity, 1%)/Tween 80 (0.01%)/water (distilled)	Mouse	PO (gavage)	91 weeks	10 mL/kg QD	None	Age 6 weeks; ♂/♀	New contributed data
27	CMC (medium viscosity, 0.5% wt/vol)/Tween 80 (0.1%, vol/vol)/water (sterile for injection, USP)	Mouse	PO (gavage)	13 weeks	10 mL/kg QD	None	Age 5 weeks; ♂/♀	New contributed data
28	CMC: 0.5%/Tween 80: 0.05%/in PBS pH 7.4	Dog	IA	2 days	0.35 mL SD	1-day postdosing, 1 animal had moderate hemorrhage of right stifle fat pad and mildly increased synovial fluid volume on necropsy, 2 had lameness 2 days postinjection, resolved within 24 hours	GLP; age 8 months; 6♂/6♀	New contributed data
29	CMC: 0.5%/Tween 80: 0.05%/in PBS pH 7.4	Dog	IA	q30d over 3 months	350 μL	None	GLP; age 5-6 months; 5♂/5♀	New contributed data
30	CMC: 0.5%/Tween 80: 0.05%/in PBS pH 7.4	Dog	IA	q30d over 9 months	350 μL	None	GLP; age 5-6 months; 5♂/5♀	New contributed data
31	Corn oil/benzyl alcohol (99:1)	Rat	PO (gavage)	1 month	1 mL/kg/d	Well tolerated	Sprague Dawley; during the first 3 days of the study, the vehicle was di(ethylene glycol)ethyl ether. From the fourth day, it was replaced by corn oil/benzyl alcohol	Contributed data, 2006
32	Corn oil/EtOH 20%	Rat	PO (gavage)	1 month	2.5 mL/kg/d	Well tolerated	Sprague Dawley	Contributed data, 2006
33	Corn oil/EtOH 20%	Rat	PO (gavage)	1 month	5 mL/kg/d	Well tolerated	Sprague Dawley	Contributed data, 2006
34	Cyclodextrin/ORA-Plus suspension	Rat	PO (gavage)	28 doses	15 mL/kg	Fecal changes (soft, watery, or mucoid); kidney lesions		Contributed data, 2006

(continued)

Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
35	Cyclodextrin/ORA-Plus suspension	Rat	PO (gavage)	SD	20 mL/kg	None		Contributed data, 2006
36	Cyclodextrin/ORA-Plus suspension	Rat	PO (gavage)	SD	20 mL/kg	None		Contributed data, 2006
37	Cyclodextrin/ORA-Plus suspension	Rat	PO (gavage)	5 doses		None		Contributed data, 2006
38	Dehydrated EtOH (200 proof): 86.249%/hexylene glycol: 10.000%/ dimethiconol blend 20: 2.500%/ hydroxypropylcellulose: 1.250%/ anhydrous citric acid: 0.001%	Minipig	Topical	28 days	5 mL QD	None	GLP; age 3-5 months; 5♂/5♀	New contributed data
39	Dextrose/trehalose (25%)	Rat	Bolus injection	28 doses	10 mL/kg	None	5% solution	Contributed data, 2006
40	Dextrose for injection (USP)/EtOH (5%)	Rat	PO (gavage)	SD		None	5% solution	Contributed data, 2006
41	Diethylacetamide/NaCl	Mouse	IV		MTD: 1.4 g/kg; LD_{50}: 2.3-3.2 g/kg; NOEL: 468 mg/kg		CD-1 mice; 30% of a 5 mL/kg dose volume at MTD; (%vol/vol) in NaCl	Sambrone[6]
42	Disodium hydrogen phosphate dihydrate (8 mmol/L)/sodium dihydrogen phosphate dihydrate (7 mmol/L)/NaCl (50 mmol/L)/sucrose (146 mmol/L)/Poloxamer 188 (0.12 mmol/L)/water (for injection, pH 6.9 $\pm$ 0.4)	Nonhuman primate	SC	26 weeks	2 mL/kg once weekly	None	Age 1-1.5 years; ♂/♀	New contributed data
43	DMSO (1.25%)/5% mannitol (5%)/ Kolliphor (1.25%)	Nonhuman primate	PO (gavage)	ADME	1 mL/kg/d	Well tolerated		Contributed data, 2006
44	DMSO (2%)/PEG 400 (10%)	Nonhuman primate	IV	1 month (ADME)	1.5 mL/kg	Well tolerated		Contributed data, 2006
45	DMSO (2%)/PEG 400 (10%)	Nonhuman primate	IV	1 week (ADME)	1.5 mL/kg	Well tolerated		Contributed data, 2006
46	DMSO (2%)/PEG 400 (10%)	Nonhuman primate	IV	2 months (ADME)	1.5 mL/kg	Well tolerated		Contributed data, 2006
47	DMSO (3.5%)/PEG 400	Nonhuman primate	PO (gavage)	Prelim	5 mL/kg/d	Soft liquid feces		Contributed data, 2006
48	DMSO (5%)/mannitol (4.5%)/ Kolliphor (5%)	Nonhuman primate	IV	2 weeks	2 mL/kg/d	Well tolerated		Contributed data, 2006
49	DMSO/NaCl	Mouse	IV		MTD: 2.2 g/kg; LD_{50}: 3.8-7.6 g/kg; NOEL: 1.6 g/kg		CD-1 mice; 40% of a 5 mL/kg dose volume at MTD; (%vol/vol) in NaCl	Sambrone[6]
50	DMSO/PEG 400 (99%)	Rat	PO (gavage)	11 doses		None	1% solution	Contributed data, 2006
51	DMSO/PEG 400 (99%)	Rat	PO (gavage)	11 doses	2 mL/kg	None	1% solution	Contributed data, 2006

(continued)

Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
52	DMSO/PEG 400/Tris buffer	Nonhuman primate	IV (bolus)	ADME	2 mL/kg	Well tolerated		Contributed data, 2006
53	DMSO/PEG 4,000/water (DI) (15/35/50)	Rat	IP	28 days	10 mL/kg	Well tolerated		Contributed data, 2006
54	DMSO/PEG 4,000/water (DI) (15/35/50)	Mouse	IP	28 days	10 mL/kg	Well tolerated		Contributed data, 2006
55	DMSO/Solutol HS15/water (pH 3-11) (20/5/75)	Rat	IV (bolus)		2 mL/kg	Well tolerated		Strickley[8]
56	DMSO/tetraglycol (50/50)	Minipig	IV	1 day	0.4 mL/kg SD	Immediate cardiac arrest; study was canceled after first dose	Age 3 months; 1♂	New contributed data
57	DMSO + 1% Tween 80 at 0.12% in water for injection	Mouse	SC	RNA extraction, 7 days	4/10 mL/kg/injection	Well tolerated		Contributed data, 2006
58	EDTA (0.2 mg/mL)/citric acid anhydrous (0.8 mg/mL)/NaCl (4.6 mg/mL, low iron)/water (sterile for injection, USP, pH 3.9-4.0)	Rat	IV (slow bolus)	13 weeks	4.5 mL/kg QD	Red/blue skin discoloration and edema of the tail (nonadverse)	Age 6 weeks; ♂/♀	New contributed data
59	EDTA pH 7.3 (phosphate 10 mmol/L; NaCl 150 mmol/L; EDTA 0.5 mmol/L)	Rat	IV (into tail vein)	1 month	0.92 mL/kg	Well tolerated	Sprague Dawley	Contributed data, 2006
60	EDTA pH 7.3 (phosphate 10 mmol/L; NaCl 150 mmol/L; EDTA 0.5 mmol/L)	Nonhuman primate	IV (into saphena vein)	2 weeks	0.92 mL/kg	Well tolerated		Contributed data, 2006
61	EtOH (190 proof): 63.37%/glycerol: 3%/Carbopol Ultrez 10: 2.5%/Tween 20: 2%/propylene glycol: 2%/panthenol: 0.15%/salicylic acid: 0.15%/EDTA: 0.05%/water (DI): 26.78%	Minipig	Topical	92 days	1 g QD	None	GLP; age 3-4 months; 5♂/5♀	New contributed data
62	EtOH/Kolliphor EL/water for injection (10/5/85)	Nonhuman primate	IV	ADME	0.4 mL/kg	Well tolerated		Contributed data, 2006
63	EtOH/Kolliphor EL/water for injection (10/5/85)	Rat	IV	ADME	2 mL/kg	Well tolerated		Contributed data, 2006
64	EtOH/NaCl	Mouse	IV		MTD: 986 mg/kg; LD_{50}: 1.6-4.3 g/kg; NOEL: 197 mg/kg		CD-1 mice; 25% of a 5 mL/kg dose volume at MTD; (%vol/vol) in NaCl	Sambrone[6]
65	EtOH/propylene glycol/water (12.5/15.5/75, vol/vol/vol)	Rat	PO (gavage)	2 weeks	5 mL/kg/d	Well tolerated		Contributed data, 2006
66	EtOH/propylene glycol/water (12.5/15.5/75, vol/vol/vol)	Rat	SC	2 weeks	2 mL/kg/d	Well tolerated		Contributed data, 2006

(continued)

Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
67	EtOH/propylene glycol/water (30/10/60)	Dog	IV		5 mL/kg at a rate of 0.3 mL/kg	Hemolyis in vitro dog blood		New contributed data
68	EtOH/propylene glycol/water (30/20/50)	Dog	IV		5 mL/kg at a rate of 0.3 mL/kg	Hemolyis in vitro dog blood		New contributed data
69	EtOH/propylene glycol/water (40/10/50)	Dog	IV		5 mL/kg at a rate of 0.3 mL/kg	Hemolyis in vitro dog blood		New contributed data
70	EtOH/Solutol HS15/water	Nonhuman primate	PO (gavage)	39 weeks	1 mL/kg/d	Well tolerated		Contributed data, 2006
71	EtOH/Solutol HS15/water	Nonhuman primate	PO (gavage)	4 weeks	1 mL/kg/d	Well tolerated		Contributed data, 2006
72	EtOH/water (30/70)	Rat	IV		5 mL/kg at a rate of 0.3 mL/kg	Hematuria		New contributed data
73	EtOH: 50%/propylene glycol: 50%/ with BHA: 0.05%/BHT: 0.05%	Minipig	Topical	16 weeks	1 mL TID	All males had increased AST at the end of the study, up to 500 IU/L (reference: 19-263 IU/L)	GLP; age 3-4 months; 6♂/6♀	New contributed data
74	Gelatin (0.5% w/v)/mannitol (5% w/v)/water for injection	Nonhuman primate	PO (gavage)	Prelim	5 mL/kg/d	Well tolerated		Contributed data, 2006
75	Gelucire/PEG 400/NMP/Transcutol HP (50/30/10/10)	Minipig	PO	4 days	5 mL/kg QD	None	Non-GLP; age 4-6 months; 3♀	New contributed data
76	Gelucire 44/14/PEG 400/NMP/ Transcutol HP (50/30/10/10)	Minipig	PO	3 days	5 mL/kg QD	Mild transient diarrhea 24-30 hours after first dose	Non-GLP; age 7-8 months; 3♀	New contributed data
77	Gelucire 44/14/PEG 400/NMP/ Transcutol HP (50/30/10/10)	Mouse	PO	5 days	5 mL/kg QD	None	Non-GLP; age 9-14 weeks; 6♂/6♀	New contributed data
78	Histidine (20 mmol/L, pH 6.5)/ sucrose (8.8%)	Rat	IV (slow bolus)	14 days	5 mL/kg QD	None	Age 6 weeks; ♂/♀	New contributed data
79	Histidine (20 mmol/L, pH 6.5)/ sucrose (8.8%)	Dog	SC	14 days	1 mL/kg QD	None	Age 5-6 months; ♂/♀	New contributed data
80	Histidine-buffered solution (10 mmol/L, pH 6.5)/NaCl (130 mmol/L)/ water (sterile)	Rat	IV (bolus)	1 day	7.14 mL/kg SD	None	Age 5 months; ♂	New contributed data
81	HPMC (0.5%)/Tween 80 (0.1%)/ water (DI)	Nonhuman primate	PO (gavage)	28 days	5 mL/kg QD	Soft/watery feces	Age 2-4 years; ♂/♀	New contributed data
82	HPMC (0.5%)/Tween 80 (5%)	Rat	PO (gavage)	2 weeks	5 or 1 mL/kg/d	Well tolerated		Contributed data, 2006
83	HPMC (1%)/Poloxamer 188 (1%)	Dog	PO	2 weeks	5 mL/kg/d	Well tolerated	Beagle	Contributed data, 2006
84	HPMC (1%)/Poloxamer 188 (1%)	Dog	PO	2 weeks	10 or 20 mL/kg/d	Well tolerated	Beagle	Contributed data, 2006
85	HPMC (1%)/Poloxamer 188 (1%)	Dog	PO	2 months	10 mL/kg/d	Well tolerated	Beagle	Contributed data, 2006
86	HPMC (1%)/Tween 80 (0.25%)/water (purified)	Rat	PO (gavage)	11 days	10 mL/kg QD	None	Age 8-10 weeks; ♀	New contributed data

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Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
87	HPMC/sodium lauryl sulfate (2%)/water (distilled)	Rat	PO (gavage)	SD	10 mL/kg	None	0.5% solution	Contributed data, 2006
88	HPMC acetate succinate (90 mg/mL)/methylcellulose (0.5%)	Mouse	PO	14 days	5 mL/kg EOD	None	GLP; age 61-63 days; 20♂/20♀	New contributed data
89	HPMC acetate succinate (90 mg/mL)/methylcellulose (0.5%)	Minipig	PO	14 days	6 mL/kg EOD	None	GLP; age 3-5 months; 5♂/5♀	New contributed data
90	HPMC: 1%/fumaric acid: 0.5%/Tween 80: 0.1%/glycerol: 0.1%/in water	Dog	PO	14 days	5 mL/kg QD	None	Non-GLP; age 7-9 months; 1♂/1♀	New contributed data
91	HPβCD (20% solution)/DMSO (99/1)	Dog	IV	ADME	4 mL/kg/d	Well tolerated		Contributed data, 2006
92	HPβCD (20%)/sodium acetate (25 mmol/L, pH 4)	Rat	PO (gavage)	28 days	5 mL/kg QD	None	Age 6 weeks; ♂/♀	New contributed data
93	HPβCD (20%)/sodium acetate (25 mmol/L, pH 4)	Nonhuman primate	PO (gavage)	28 days	2.5 mL/kg/dose BID	None	Age 2-3.5 years; ♂/♀	New contributed data
94	HPβCD (30%)/DMSO (5%)/water (purified) (acidic solution, wt/wt)	Nonhuman primate	IV	4 weeks	1 mL/kg/d	Well tolerated		Contributed data, 2006
95	HPβCD/citric acid solution (0.05 mol/L)	Dog	PO (gavage)	14 doses	3 mL/kg	None	20% solution	Contributed data, 2006
96	HPβCD/NaCl solution (0.9%)	Dog	IV	SD	1 mL/kg	None	10% solution	Contributed data, 2006
97	HPβCD/NaCl solution (0.9%)	Rat	IV	SD	1 mL/kg	None	10% solution	Contributed data, 2006
98	HPβCD: 12%/EtOH: 8%/propylene glycol: 2%/water for injection	Dog	IV (1-hour infusion)	q7d × 3 doses over 16 days	2 mL/kg	May cause temporary mild diarrhea	Non-GLP; age 1-4 years; 2♂/2♀	New contributed data
99	HPβCD: 12%/EtOH: 8%/propylene glycol: 2%/water for injection	Dog	IV (1-hour infusion)	q7d × 3 doses over 16 days	1.5 mL/kg	May cause diarrhea	Non-GLP; age 1-4 years; 2♂/2♀	New contributed data
100	Hydroxyethylcellulose (1%)/Tween 80 (0.25%)/Antifoam (0.05%)/water (purified)	Rat	PO (gavage)	1 day	10 mL/kg SD	None	Age 6 weeks; ♂	New contributed data
101	Hydroxyethylcellulose (1%, wt/vol)/Tween 80 (0.25%)/Antifoam 1510-US (0.05%)/water (purified)	Rat	PO (gavage)	4 days	10 mL/kg QD	None	Age 8-9 weeks; ♀	New contributed data
102	Hymetellose (1%)/Poloxamer 188 (0.1%)	Rabbit	PO (gavage)	1 month	3 mL/kg/d	Well tolerated		Contributed data, 2006
103	Imwitor 742/Tween 80 (1:1, wt/wt)	Rat	PO (gavage)	7 days	10 mL/kg QD	None	Age 7 weeks; ♂/♀	New contributed data
104	Imwitor 742/Tween 80 (1:1, wt/wt)	Nonhuman primate	PO (gavage)	7 days	5 mL/kg QD	Soft/watery feces	Age 2-3 years; ♂/♀	New contributed data
105	Imwitor 742/Tween 80 (1:1, wt/wt)	Hamster	PO (gavage)	7 days	5 mL/kg QD	None	Age 5 weeks; ♂/♀	New contributed data
106	Kolliphor EL/PEG 300 (4:1, wt/wt)	Mouse	PO (gavage)	104 weeks	3 mL/kg/d	Well tolerated		Contributed data, 2006
107	Kolliphor RH40: 41.5%/PEG 400: 20%/TPGS: 20%/propylene glycol: 10%/Tween 80: 8.5%	Rat	PO (gavage)	92 days	10 mL/kg QD	None	Age 10-23 weeks; ♂/♀	New contributed data

(continued)

Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
108	Kolliphor EL/10% 190 proof EtOH/ 80% 5% dextrose in water (D5W)	Rabbit	IV	SD	5 mL/kg	None	10% solution	Contributed data, 2006
109	Kolliphor EL/10% 190 proof EtOH/ 80% 5% dextrose in water (D5W)	Rabbit	IV	SD	5 mL/kg	Local irritation, very slight to well-defined erythema	10% solution	Contributed data, 2006
110	Kolliphor EL/10% 190 proof EtOH/ 80% 5% dextrose in water (D5W)	Rabbit	Perivascular injection	SD	0.5 mL/kg	None	10% solution	Contributed data, 2006
111	Kolliphor EL/10% 190 proof EtOH/ 80% 5% dextrose in water (D5W)	Rabbit	Perivascular injection	SD	0.5 mL/kg	Erythema	10% solution	Contributed data, 2006
112	Labrafil/Tween 80 (0.1%)	Rat	PO (gavage)	2 doses	2 mL/kg/dose	None		Contributed data, 2006
113	Labrasol/Kolliphor HS15/Transcutol HP (60/30/10)	Minipig	PO (gavage)	Once weekly over 4 weeks	3.75 mL/kg	None	Age 6-7 months; ♂/♀	New contributed data
114	Labrasol/Labrafil/Transcutol	Rat	PO	4 weeks	0, 5, 10, or 20 mL/ kg/d	Tolerated at 5 mL/kg/d	Changes in appearance and behavior at 10 mL/ kg/d; lethality and renal and hepatic effects at 20 mL/kg/d; Wistar rats	Sullivan et al[328]
115	Labrasol/PEG-400 (60/40)	Rat	PO	7 days	5 mL/kg BID	Well tolerated	Sprague Dawley rats (Harlan) age ~8-10 weeks; ♂/♀	New contributed data
116	Lactated Ringer injection (USP)	Nonhuman primate	IV	28 days	2 mL/kg QD	None		Contributed data, 2006
117	L-Ascorbic acid/isotonic NaCl	Rat	PO	90 days	500 g/kg	Hematologic changes, weight loss		Gad et al[2]
118	Mannitol (47 mg/mL)/succinic acid (1.181 mg/mL)/water (Sterile, USP)	Dog	SC	28 days	0.1 mL/kg QD	None	Age 5 months; ♂/♀	New contributed data
119	Mannitol (5%)/acetate buffer pH4 (4:6)	Minipig	IM	Tolerance	0.8 or 1.2 mL/kg/d	Well tolerated		Contributed data, 2006
120	Mannitol (5%)/gelatin (0.5%)/Tween 80 (0.2%; aqueous solution, % w/v)	Nonhuman primate	PO (gavage)	2 weeks	2 mL/kg/d	Well tolerated		Contributed data, 2006
121	Mannitol: 120 mg/Na_2HPO_4: 12 mg/ NaCl: 10.5 mg/water: 4 mL	Dog	IV	1 week (placebo), then 1 day (with the test item)	0.15 mL/kg	Well tolerated	Beagle dogs	Contributed data, 2006
122	Mannitol: 250 mmol/L/sodium succinate: 25 mmol/L/water pH 4.9	Rat	SC	28 days	4 mL/kg	Well tolerated		Contributed data, 2006
123	Mannitol: 250 mmol/L/sodium succinate: 25 mmol/L/water pH 4.9	Mouse	SC	28 days	20 mL/kg	Well tolerated		Contributed data, 2006
124	Methane sulfonic acid (5%)/EtOH (5%)/water	Rat	PO	28 days	10 mL/kg	Well tolerated		Contributed data, 2006
125	Methocel (0.5%)/Tween 80 (0.1%)/ water (reverse osmosis)	Rat	PO (gavage)	182 days	10 mL/kg QD	None	Age 6 weeks; ♀	New contributed data

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Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
126	Methocel (A4M Premium, 0.5%)/ simethicone (0.1%)/TPGS (10%)/ citrate buffer (17 mmol/L, pH 4 ± 0.05)	Rat	PO (gavage)	28 days	10 mL/kg QD	None	Age 8 weeks; ♂/♀	New contributed data
127	Methyl methacrylate/glycol dimethacrylate cross polymer, propylene glycol dicaprylate/ dicaprate, BHT	Rat	Topical	90 days	2.4 mL/kg × 44-46 d, then 0.75 mL/kg QD	None	GLP; age 8 weeks; 15♂/ 15♀	New contributed data
128	Methyl paraben, propyl paraben	Minipig	Topical	91 days	0.05 mL/cm^2 TID	None	Age 2-3 months; 6♂/6♀	New contributed data
129	Methylcellulose (0.5% wt/vol)/Tween 80 (0.1%)	Guinea Pig	PO	28 days	10 mL/kg	Well tolerated		Contributed data, 2006
130	Methylcellulose (aqueous, 0.5% wt/ wt)/Tween 80 (0.5% wt/wt)	Rat	PO (gavage)	Prelim/segment III	5 mL/kg/d	Well tolerated		Contributed data, 2006
131	Methylcellulose/PEG 200 (5%)	Rat	PO (gavage)	SD	10 mL/kg	None	0.5% solution	Contributed data, 2006
132	Methylcellulose/Tween 80 (0.1% vol/ vol)	Rat	PO (gavage)	SD	7.5 mL/kg	None	0.5% solution	Contributed data, 2006
133	Methylcellulose/Tween 80 (0.1% vol/ vol)	Rat	PO (gavage)	SD	5 mL/kg	None	0.5% solution	Contributed data, 2006
134	Methylcellulose/Tween 80 (0.1% vol/ vol)	Rat	PO (gavage)	28 doses	5 mL/kg/dose	None	0.5% solution	Contributed data, 2006
135	Methylcellulose/Tween 80 (0.1% vol/ vol)	Dog	PO (gavage)	28 doses	1 mL/kg/dose	None	0.5% solution	Contributed data, 2006
136	Methylcellulose/Tween 80 (0.1% vol/ vol)	Dog	PO (gavage)	SD	5 mL/kg/dose	None	0.5% solution	Contributed data, 2006
137	Methylcellulose/Tween 80 (0.1%)	Rat	PO (gavage)	SD	10 mL/kg	None	0.5% solution	Contributed data, 2006
138	Methylcellulose 1,500 cP (0.5%)/ Tween 80 (0.1%)/acetate buffer (10 mmol/L)/water (distilled, pH 4.5 ± 0.1)	Mouse	PO (gavage)	28 days	10 mL/kg QD	None	Age 6 weeks; ♂/♀	New contributed data
139	Methylcellulose 1,500 cP (0.5%)/ Tween 80 (0.1%)/acetate buffer (10 mmol/L)/water (distilled, pH 4.5 ± 0.1)	Mouse	PO (gavage)	13 weeks	10 mL/kg QD	None	Age 6 weeks; ♂/♀	New contributed data
140	Methylcellulose 1,500 cP (0.5%)/ Tween 80 (0.1%)/acetate buffer (10 mmol/L)/water (distilled, pH 4.5 ± 0.1)	Nonhuman primate	PO (gavage)	91 days	5 mL/kg QD	None	Age 2-4 years; ♂/♀	New contributed data
141	Methylcellulose 1,500 cP (0.5%)/ Tween 80 (0.1%)/acetate buffer (10 mmol/L)/water (distilled, pH 4.5 ± 0.1)	Rat	PO (gavage)	91 days	10 mL/kg QD	None	Age 6 weeks; ♂/♀	New contributed data

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Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
142	Methylcellulose 400 cP (0.5%)/ sodium lauryl sulfate (0.5%)	Rat	PO (gavage)	26 weeks	10 mL/kg QD	None	Age 6 weeks; ♂/♀	New contributed data
143	Methylcellulose 400 cP (0.5%)/ sodium lauryl sulfate (0.5%)/ simethicone (0.01%)/water (DI; % wt/ vol)	Rat	PO (gavage)	13-26 weeks	5 mL/kg QD	None	Age 8 weeks; ♂/♀	New contributed data
144	Methylcellulose 400 cP (0.5%)/ sodium lauryl sulfate (0.5%)/water (DI)	Dog	PO (gavage)	26 weeks	5 mL/kg QD	Soft/watery feces (nonadverse)	Age 4-5 months; ♂/♀	New contributed data
145	Methylcellulose 400 cP (0.5%)/ sodium lauryl sulfate (0.5%)/water (DI)	Dog	PO (gavage)	52 weeks	5 mL/kg QD	Soft/watery feces (nonadverse)	Age 4-5 months; ♂/♀	New contributed data
146	Methylcellulose 400 cP (0.5%)/ sodium lauryl sulfate (0.5%)/water (DI)	Rat	PO (gavage)	28 days	10 mL/kg QD	None	Age 8 weeks; ♂/♀	New contributed data
147	Methylparaben (0.17%)/ propylparaben (0.03%)/acetyl cysteine (0.5%)/in citrate buffer (100 mmol/L, pH 6.5)/sodium hydroxide (10%) added to pH 6.0	Minipig	SC	56 days	0.138 mL/kg QD	Temporary dose site irritation postinjection, resolved within a few minutes	GLP; age 4-7 months; 3♂/3♀	New contributed data
148	NaCl (0.9 5)/propylene glycol/EtOH (50/40/10)	Dog	IV		5 mL/kg at a rate of 0.3 mL/kg	Hemolysis in vitro dog blood		New contributed data
149	NaCl (0.9%)/EtOH (60/40)	Rat	IV		5 mL/kg at a rate of 0.3 mL/kg	Hematuria		New contributed data
150	NaCl (0.9%)/EtOH (70/30)	Rat	IV		5 mL/kg at a rate of 0.3 mL/kg	Hematuria		New contributed data
151	NaCl (0.9%)/EtOH/PEG 400 (50/30/ 20)	Dog	IV		5 mL/kg at a rate of 0.3 mL/kg	Partial hemolysis in vitro dog blood, RBC discolored		New contributed data
152	NaCl (0.9%)/EtOH/PEG 400 (50/40/ 10)	Dog	IV		5 mL/kg at a rate of 0.3 mL/kg	Partial hemolysis in vitro dog blood, RBC discolored		New contributed data
153	NaCl (0.9%)/EtOH/propylene glycol (60/30/10)	Dog	IV		5 mL/kg at a rate of 0.3 mL/kg	Hemolysis in vitro dog blood		New contributed data
154	NaCl (0.9%)/EtOH/propylene glycol (50/30/20)	Dog	IV		5 mL/kg at a rate of 0.3 mL/kg	Hemolysis in vitro dog blood		New contributed data
155	NaCl (0.9%)/EtOH/propylene glycol (50/40/10)	Dog	IV		5 mL/kg at a rate of 0.3 mL/kg	Hemolysis in vitro dog blood		New contributed data
156	NaCl (0.9%)/propylene glycol/EtOH (50/30/20)	Dog	IV		5 mL/kg at a rate of 0.3 mL/kg	Hemolysis in vitro dog blood		New contributed data

(continued)

Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
157	NaCl/DMSO/tetraglycol (90/5/5)	Rat	IV	14 days	4.3 mL/kg SD	None	GLP; age 8 weeks; 5♂/5♀	New contributed data
158	NaCl/DMSO/tetraglycol (90/5/5)	Minipig	IV	16 days	2.6 mL/kg SD	None	GLP; age 2-4 months; 1♂/1♀	New contributed data
159	NaCl for injection (USP)/mannitol (20 mg/mL)/Tween 80 (4 mg/mL), sterile filtered	Rat	IV (infusion)	SD	6.67 mL/kg/dose	None	0.9% solution	Contributed data, 2006
160	NaCl for injection, USP/10% EtOH in 0.9%	Dog	IV (bolus)	SD	5 mL/kg	None	10% solution	Contributed data, 2006
161	NaCl for injection/10% EtOH	Rat	IV	SD	5 mL/kg	None	10% solution	Contributed data, 2006
162	NaCl for injection/20% PET in 0.9%	Rat	IV (slow bolus)	7 doses	0.6 mL/kg	None	20% solution	Contributed data, 2006
163	NaCl USP: 15.00%/potassium chloride: 7.50%/L-arginine HCl USP: 7.50%/glyceryl stearate SE: 7.00%/cetyl alcohol NF: 7.00%/propylene glycol: 5.00%/squalane NF: 4.00%/Tween 20 NF: 2.00%/sodium hydroxide: 1.30%/oleic acid NF: 1.00%/isopropyl myristate: 1.00%/Keltrol RD: 0.50% (xanthan gum)/Keltrol BT: 0.30% (xanthan gum)/water (purified): 40.90%	Minipig	Topical	7 days	3.0 g/kg BID	Severe dose site erythema in 2 of 6 animals	GLP; age 3-5 months; 3♂/3♀	New contributed data
164	Neobee 1053 Oil/EtOH/BHT (94.95/5/0.05)	Mouse	IV	28 days	10 mL/kg	Well tolerated		Contributed data, 2006
165	Neobee 1053 Oil/EtOH/BHT (94.95/5/0.05)	Rat	PO	28 days	5 mL/kg	Well tolerated		Contributed data, 2006
166	NMP/NaCl	Mouse	IV		MTD: 1.3 g/kg; LD_{50}: 54-3,600 mg/kg; NOEL: 257 mg/kg		CD-1 mice; 25% of a 5 mL/kg dose volume at MTD; (%vol/vol) in NaCl	Sambrone[6]
167	Octoxynol-40, vitamin E	Dog	Ocular (topical)	q1h × 8 doses over 14 days	0.35 µL (1 drop)/eye	None	GLP; age 8 months; 4♂/6♀	New contributed data
168	Octoxynol-40, vitamin E	Rabbit	Ocular (topical)	q1h × 8 doses over 14 days	0.35 µL (1 drop)/eye	None	GLP; age 5-6 months; 5♂/5♀	New contributed data
169	Octoxynol-40, vitamin E	Rabbit	Ocular (topical)	q1h × 8 doses over 13 weeks	0.35 µL (1 drop)/eye	None	GLP; age 6 months; 6♂/6♀	New contributed data
170	Oleic acid/PEG 400/Kolliphor EL (80/10/10, wt/wt)	Dog	PO (capsule)	9 months	0.6 mL/kg QD	None	Age 6 months; ♂/♀	New contributed data
171	Oleic acid/PEG 400/Kolliphor EL (80/10/10, wt/wt)	Rat	PO (gavage)	104 weeks	2 mL/kg QD	Decreases in body weight gain (nonadverse)	Age 4 weeks; ♂/♀	New contributed data

(continued)

Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
172	Oleic acid/PEG 400/Kolliphor EL (80/10/10, wt/wt)	Mouse	PO (gavage)	13 weeks	2 mL/kg QD	None	Age 6 weeks; ♂/♀	New contributed data
173	Oleic acid/PEG 400/Kolliphor EL (80/10/10, wt/wt)	Nonhuman primate	PO (gavage)	14 days	2 mL/kg/dose BID	Emesis and fecal changes	Age 2-3 years; ♂/♀	New contributed data
174	Olive oil: 28.25%/Tween 80: 11.25%-13.5%/oleyl alcohol NF: 10.00%/lanolin alcohol NF: 8.00%/cyclomethicone NF: 3.00%/cetyl acetate: 1.5%-3.75%/shea butter: 2.00%/0.50% sorbitan tristearate/acetylated lanolin alcohol: 0.15%-0.75%/methylparaben NF: 0.20%/propylparaben NF: 0.05%/water (USP Purified): 33.00%	Minipig	Topical	14 days	0.32 mL/kg QD	4 of 6 experienced persistent mild (Draize score 1/4) dose site erythema or miliary (disseminated in surrounding cutis) erythema	GLP; age 3-5 months; 5♂/5♀	New contributed data
175	Peanut oil/EtOH 100 (8:1)	Dog	SC		0.33 mL/kg	Well tolerated	Beagle	Contributed data, 2006
176	Peceol (Gattefossé)/Tween 80/PEG 400/vitamin E (TPPE; 50/40/10/0.2)	Rat	PO (gavage)	91 days	10 mL/kg/dose BID	None	Age 6 weeks; ♂/♀	New contributed data
177	Peceol (Gattefossé)/Tween 80/PEG 400/vitamin E (TPPE; 50/40/10/0.2)	Dog	PO (gavage)	91 days	5 mL/kg/dose BID	None	Age 7-8 months; ♂/♀	New contributed data
178	PEG (5%)/methylcellulose (0.5%)	Pig	PO (gavage)	28 doses	5 mL/kg	None	5% solution	Contributed data, 2006
179	PEG/DAM (70/30, vol/vol)	Dog	IV	2 weeks	0.32 mL/kg for single IV injection	Well tolerated		Gad et al[2]
180	PEG/DAM (70/30, vol/vol)	Rat	IV	3 week	Bolus 0.8-1.07 mL/kg, infusion 0.266-0.356 mL/kg, intravenous injection (into tail vein) following by an intravenous injection for 6 hours	Well tolerated		Gad et al[2]
181	PEG/DAM (70/30, vol/vol)	Dog	IV (into cephalic of saphenous vein) following by an IV injection for 6 hours	2 weeks	Bolus 0.24-0.33 mL/kg, infusion 0.08-0.11 mL/kg/h	Well tolerated		Gad et al[2]

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Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
182	PEG/DAM (70/30, vol/vol)	Rat	IV	3 weeks	Bolus 0.8-1.07 mL/kg, infusion 0.266-0.356 mL/kg, intravenous injection (into tail vein) following by an intravenous injection for 6 hours	Well tolerated		Gad et al[2]
183	PEG 200/95% methylcellulose (0.5%)	Rat	PO	3 doses	5 mL/kg of body weight	None	5% solution	Contributed data, 2006
184	PEG 200/EtOH/dextrose (5%; 70/15/15, vol/vol/vol)	Minipig	IV	2 weeks	1 mL/kg	Well tolerated		Contributed data, 2006
185	PEG 300 (40%)/Cavisol W7 (25/75 vol/vol)	Dog	PO	28 days	10 mL/kg	Well tolerated		Contributed data, 2006
186	PEG 300 (40%)/Cavisol W7 (25/75 vol/vol)	Rat	PO	28 days	10 mL/kg	Well tolerated		Contributed data, 2006
187	PEG 300/DMA (90/10)	Rat	PO (gavage)	14 days	2.5 mL/kg QD	None	Age 6 weeks; ♂/♀	New contributed data
188	PEG 300/DMA (90/10)	Dog	PO (gavage)	14 days	2.5 mL/kg QD	Body weight loss (>20%; adverse)	Age 5-6 months; ♂/♀	New contributed data
189	PEG 300/NaCl (0.9%; 40/60, vol/vol)	Rat	PO (gavage)	ADME	5 mL/kg/d	Well tolerated		Contributed data, 2006
190	PEG 300/propylene glycol/water (DI; 55/25/20)	Rat	PO (gavage)	7 days	10 mL/kg QD	None	Age 9-10 weeks; ♂/♀	New contributed data
191	PEG 400/Captisol/EtOH/water (pH 3; 45/7/5/43)	Dog	IV (infusion)		1 mL/kg	Well tolerated		Strickley[8]
192	PEG 400/DMA (50/50)	Dog	IV (infusion)		0.1 mL/kg	Well tolerated		Strickley[8]
193	PEG 400/DMSO (20%)	Mouse	IV (into tail vein)	Acute	1,128 mg/kg (dose volume 5 mL/kg)	NOEL	20% PEG 400	Thackaberry[252]
194	PEG 400/DMSO (20%)	Mouse	IV (into tail vein)	Acute	3,948 mg/kg (dose volume 5 mL/kg)	MTD; ventral recombency, ataxia, tremors, and hypoactivity shortly after dosing. Tremors for up to 4 minutes, hypoactivity for up to 10 minutes is typical	70% PEG 400	Thackaberry[252]
195	PEG 400/DMSO (95/5)	Rabbit	PO (gavage)	12 doses	0.33 mL/kg	None	5% solution	Contributed data, 2006
196	PEG 400/EtOH (10%)/DMSO (10%)	Mouse	IV (into tail vein)	Acute	1,692 mg/kg (dose volume 5 mL/kg)	NOEL	30% PEG 400	Thackaberry[252]

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Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
197	PEG 400/EtOH (10%)/DMSO (10%)	Mouse	IV (into tail vein)	Acute	2,820 mg/kg (dose volume 5 mL/kg)	MTD; ventral recumbency, tremors, ataxia, and hypoactivity shortly after dosing, recovery by 10 minutes is typical	50% PEG 400	Thackaberry[252]
198	PEG 400/EtOH (20%)	Mouse	IV (into tail vein)	Acute	3,384 mg/kg (dose volume 5 mL/kg)	MTD; vocalization and struggling at dosing, ventral recumbency, rapid breathing, tremors, and ataxia shortly after dosing, recovery by 5 minutes is typical	60% PEG 400	Thackaberry[252]
199	PEG 400/EtOH (200 proof; 95/5, vol/vol)	Rat	PO	14 days	10 mL/kg BID	Abnormal clinical observations included anogenital or urogenital staining, soft feces/watery diarrhea, stained body surface, apparent dehydration, staining around mouth or nose/nares, and wet body surface	Wistar Han (CRL) rats; age ~8-10 weeks at study initiation; ♂/♀	New contributed data
200	PEG 400/EtOH/propylene glycol/water (sterile; 30/20/20/30)	Rat	IP	7 days	2 mL/kg QD	None	Non-GLP; age 7-8 weeks; 6♂	New contributed data
201	PEG 400/EtOH/water (pH 3-11; 45/5/50)	Rat	IV (bolus)		2 mL/kg	Well tolerated		Strickley[8]
202	PEG 400/EtOH/water (pH 3-11; 45/5/50)	Rat	IV (infusion)		5 mL/kg	Well tolerated		Strickley[8]
203	PEG 400/EtOH/water (pH 3-11; 45/5/50)	Dog	IV (bolus)		1 mL/kg	Well tolerated		Strickley[8]
204	PEG 400/EtOH/water (pH 3-11; 45/5/50)	Dog	IV (infusion)		2 mL/kg	Well tolerated		Strickley[8]
205	PEG 400/EtOH/water (sterile; 1:1:1)	Guinea pig	IV	28 days	2 mL/kg	Well tolerated		Contributed data, 2006

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Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
206	PEG 400/Kolliphor RH40 (70/30)	Rat	PO (gavage)	91 days	10 mL/kg/dose	Sporadic incidence of fecal changes (soft and/or loose/watery); slight brown/orange staining around anus; fluid contents in the cecum; 10% decrease in mean body weights (male rats); lowered food consumption; mildly increased serum urea; minimally decreased serum sodium and chloride values (male rats); minimally increased total serum cholesterol values (females); alterations in urine electrolytes; organ weight changes; minimal, focal, or multifocal coagulative hepatocellular necrosis (in 3 females and 1 male)	6♂/6♀	Stokes et al[180]
207	PEG 400/Kolliphor RH40 (90/10)	Dog	PO (gavage)	28 days	2 mL/kg/dose	Emesis; administration associated with minimal lamina propria hemorrhage in gastric glandular mucosa in 1 of 3 dogs	Beagle dogs; ♂	Stokes et al[180]
208	PEG 400/Kolliphor RH40 (90/10)	Dog	PO (gavage)	28 days	5 mL/kg/dose	Fecal alterations (loose/watery, mucoid, or red) present beginning on day 1; emesis; administration associated with minimal lamina propria hemorrhage in gastric glandular mucosa in 2 of 3 dogs; single/multifocal red areas in stomach; minimal increase in group mean serum urea	Beagle dogs; ♂	Stokes et al[180]
209	PEG 400/Labrasol/Kolliphor EL (50/30/20)	Mouse	PO (gavage)	182 days	10 mL/kg QD	Unkempt appearance (potential effect)	Age 6 weeks; ♂/♀	New contributed data

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Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
210	PEG 400/NaCl	Mouse	IV		MTD: 4.5 g/kg; LD_{50}: 8.6-9.7; NOEL: 1.7 g/kg	Over tested range, expect hypoactivity, tremors, and mild ataxia with increasing duration with dose	CD-1 mice; 80% of a 5 mL/kg dose volume at MTD; (%vol/vol) in NaCl	Sambrone[6]
211	PEG 400/NaCl (0.9%)/EtOH (50/40/10)	Dog	IV		5 mL/kg at a rate of 0.3 mL/kg	Partial hemolysis in vitro dog blood, RBC discolored		New contributed data
212	PEG 400/propylene glycol/EtOH/water (pH 3; 40/20/5/35)	Dog	IV (infusion)		2.5 mL/kg	Well tolerated		Strickley[8]
213	PEG 400/propylene glycol/Tween 80/water (25/15/6/54)	Rat	IV	28 days	10 mL/kg	Well tolerated		Contributed data, 2006
214	PEG 400/propylene glycol/Tween 80/water (25/15/6/54)	Guinea pig	IV	28 days	10 mL/kg	Well tolerated		Contributed data, 2006
215	PEG 400/propylene glycol/Tween 80/water (25/15/6/54)	Mouse	IV	28 days	10 mL/kg	Well tolerated		Contributed data, 2006
216	PEG 400/PVP K30/TPGS (90/5/5)	Dog	PO (gavage)	28 doses	2.5 mL/kg/d	None	90% solution	Contributed data, 2006
217	PEG 400/PVP K30/TPGS (90/5/5)	Rat	PO (gavage)	28 doses	5 mL/kg/d	None	90% solution	Contributed data, 2006
218	PEG 400/Solutol HS15 (70/30)	Rat	PO (gavage)	91 days	10 mL/kg	Males: sporadic fecal changes (soft and/or loose/watery); slight brown/orange staining around anus; 6% decrease in mean body weight; lower food consumption; organ weight changes; increased urine volume; alterations in urine electrolytes (both genders); fluid contents in the cecum (both genders)	6♂/6♀	Stokes et al[180]
219	PEG 400/Solutol HS15 (70/30)	Dog	PO (gavage)	28 days	2 mL/kg/dose	Intermittent loose/watery feces; sporadic emesis starting on day 1; 1 of 3 animals had minimal mucus cell hypertrophy of the ileal mucosa (direct effect of vehicle or effect of loose stools?)	Beagle dogs; 3♀	Stokes et al[180]

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Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
220	PEG 400/Solutol HS15 (70/30)	Dog	PO (gavage)	28 days	5 mL/kg/dose	Consistent incidence of loose/watery feces starting on day 1; sporadic emesis starting on day 1; 2 of 3 animals had minimal mucus cell hypertrophy of the ileal mucosa (direct effect of vehicle or effect of loose stools?); increase in RBC mass; decrease in urine volume	Beagle dogs; 3♀	Stokes et al[180]
221	PEG 400/Solutol HS15 (90/10)	Dog	PO (gavage)	28 days	2 mL/kg/dose	Intermittent loose/watery feces; sporadic emesis starting on day 1	Beagle dogs; 3♀	Stokes et al[180]
222	PEG 400/Solutol HS15 (90/10)	Dog	PO (gavage)	28 days	5 mL/kg/dose	Consistent incidence of loose/watery feces starting on day 1; sporadic emesis starting on day 1; all had minimal mucus cell hypertrophy of the ileal mucosa (direct effect of vehicle or effect of loose stools?)	Beagle dogs; 3♀	Stokes et al[180]
223	PEG 400/TPGS/PVP VA 64/EtOH (80/10/5/5)	Rat	PO (gavage)	182 days	2 mL/kg QD	White feces (nonadverse)	Age 8 weeks; ♂/♀	New contributed data
224	PEG 400/TPGS/PVP VA 64/EtOH (80/10/5/5)	Dog	PO (gavage)	9 months	1 mL/kg QD	None	Age 10-11 months; ♂/♀	New contributed data
225	PEG 400/Tween 20/Poloxamer 124 (70/20/10)	Rat	PO (gavage)	26 weeks	2 mL/kg/dose BID	None	Age 6 weeks; ♂/♀	New contributed data
226	PEG 400/Tween 20/Poloxamer 124 (70/20/10)	Dog	PO (gavage)	26 weeks	0.5 mL/kg/dose BID	None	Age 6.5-7.5 months; ♂/♀	New contributed data
227	PEG 400/Tween 20/TPGS/ Poloxamer 124 (50/20/20/10)	Mouse	PO (gavage)	91 days	2 mL/kg QD	None	Age 6 weeks; ♂/♀	New contributed data
228	PEG 400/Tween 20/TPGS/ Poloxamer 124 (50/20/20/10)	Dog	PO (capsule)	91 days	≤5 mL of vehicle QD	Soft/watery feces (nonadverse)	Age 6-7 months; ♂/♀	New contributed data
229	PEG 400/Tween 80 (95/5)	Mouse	PO	2-year Carcinogenicity	5 mL/kg BID	During the early stages of the study, a number of mice receiving the vehicle developed gastrointestinal atony, resulting in severe bloating and sometimes death	CD-1 (Harlan) mice age ~7 weeks at study initiation; ♂/♀	New contributed data

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Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
230	PEG 400/Tween 80 (95/5)	Rat	PO	2-year Carcinogenicity	5 mL/kg BID	Well tolerated	Vacuolation of the tubular epithelium in the kidney associated with PEG-linked proteins; Sprague Dawley (Harlan) rats age ~6 weeks at study initiation; ♂/♀	New contributed data
231	Phosal 53 MCT/PEG 400/Poloxamer 124/Kolliphor RH40 (40/20/20/20)	Rat	PO (gavage)	99 weeks	2 mL/kg QD	None	Age 6-110 weeks; ♂/♀	New contributed data
232	Phosphate (50 mmol/L)/NaCl (100 mmol/L)/Tween 80 (0.01%)	Nonhuman primate	SC	Prelim/2 weeks	1 mL/kg/injection	Well tolerated		Contributed data, 2006
233	Phosphate buffer 0.5 mol/L at pH 7.5/ 0.4% mannitol	Rat	SC	Segment I	0.5 mL/animal/ injection	Well tolerated		Contributed data, 2006
234	Polawax: 4.80%/alcohol denatured SDA 40-2 (190 proof): 4.25%/ propylene glycol: 4.00%/isopropyl myristate: 2.50%/sodium hydroxide solution (10.0): 1.20%/ phenoxyethanol: 1.00%/Carbomer 974P: 0.55%/water (purified): 81.7%	Minipig	Topical	210 days	0.4 g/kg QD	None	GLP; age 3 months; 5♂/ 5♀	New contributed data
235	Polawax: 4.80%/propylene glycol: 4.00%/EtOH 200 proof: 4.00%/ ispropyl myristate: 2.50%/sodium hydroxide 10% solution in purified water: 1.20%/phenoxyethanol: 1.00%/Carbomer 974P: 0.55%	Mouse	Topical	90 days	3.4 mL/kg QD	None	GLP; age 7-8 weeks; 18♂/18♀	New contributed data
236	Poloxamer 188 (0.5%)/NaCl for injection (USP, 0.9%)	Rat	SC	SD	2.5 mL/kg	None	Age 6 weeks; ♂/♀	New contributed data
237	Poloxamer 188 (0.5%)/NaCl for injection (USP, 0.9%)	Minipig	SC		1 mL/kg	None	Gottingen Minipigs age 5 months; ♂/♀	New contributed data
238	Poloxamer 188 (1%, wt/vol)/citrate buffer (100 mmol/L, pH 3)	Rat	PO (gavage)	14 days	10 mL/kg QD	None	Age 6 weeks; ♂/♀	New contributed data
239	Propylene glycol (USP)/glycerol (USP)/EtOH (200 Proof, USP; 65/25/ 10, wt/wt/wt)	Rabbit	SC	2×/wk over 3 weeks	1 mL/kg	None	Age 6.5 months; ♂/♀	New contributed data
240	Propylene glycol (USP)/glycerol (USP)/EtOH (200 proof, USP; 65/25/ 10, wt/wt/wt)	Nonhuman primate	SC	1×/wk over 3 weeks	0.5 mL/kg	Scratching and red skin discoloration at the dose site (nonadverse)	Age 3-6 years; ♂/♀	New contributed data
241	Propylene glycol/Capmul PG8/EtOH/ water (75/12.5/10/2.5)	Dog	PO (gavage)	7 days	5 mL/kg QD	None	Age 5 months; ♂/♀	New contributed data

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Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
242	Propylene glycol/Capmul PG8/EtOH/water (75/12.5/10/2.5)	Rat	PO (gavage)	21 days	10 mL/kg QD	Aspiration, salivation, material around the mouth/nose, audible breathing, stereotypical behavior (scratching in the cage following dosing), death	Consistency of vehicle considered to have contributed to aspiration risk and related observations in the rat; age 6-9 weeks; ♂/♀	New contributed data
243	Propylene glycol/EtOH/water (20/5/75)	Rat	IV (bolus)		1 mL/kg	Well tolerated		Strickley[8]
244	Propylene glycol/EtOH/water (30/20/50)	Dog	IV		5 mL/kg at a rate of 0.3 mL/kg	Hemolyis in vitro dog blood		New contributed data
245	Propylene glycol/EtOH/water (50/10/40)	Dog	IV	14 days	4 mL/kg/d at a rate of 6 mL/min	Frank red urine after first dose, this was occasionally observed throughout the 2-week period, decreases in hematocrit, hemoglobin, and erythrocyte count. Urinalyses were positive for occult blood, bilirubin, ketones, and proteins. Swelling at injection site		New contributed data
246	Propylene glycol/EtOH/water (60/20/20)	Dog	IV (bolus)		0.5 mL/kg	Well tolerated		Strickley[8]
247	Propylene glycol/EtOH/water (pH 3-11; 40/5/55)	Rat	IV (bolus)		2 mL/kg	Well tolerated		Strickley[8]
248	Propylene glycol/EtOH/water (pH 3-11; 40/5/55)	Rat	IV (infusion)		5 mL/kg	Well tolerated		Strickley[8]
249	Propylene glycol/EtOH/water (pH 3-11; 40/5/55)	Dog	IV (bolus)		1 mL/kg	Well tolerated		Strickley[8]
250	Propylene glycol/EtOH/water (pH 3-11; 40/5/55)	Dog	IV (infusion)		2 mL/kg	Well tolerated		Strickley[8]
251	Propylene glycol/NaCl	Rat	PO (gavage)	4 weeks	2 mL/kg/d	Well tolerated		Contributed data, 2006
252	Propylene Glycol/NaCl	Mouse	IV		MTD: 1.5 g/kg; LD_{50}: 5.0-8.6 g/kg; NOEL: 1 g/kg		CD-1 mice; 30% of a 5 mL/kg dose volume at MTD; (%vol/vol) in NaCl	Sambrone[6]
253	Propylene glycol/NaCl (0.9%)/EtOH (50/40/10)	Dog	IV		5 mL/kg at a rate of 0.3 mL/kg	Hemolysis in vitro dog blood		New contributed data
254	Propylene glycol/PEG 400/water/EtOH (40/25/25/10)	Nonhuman primate	PO (gavage)	4 weeks	2 mL/kg/d	Well tolerated		Contributed data, 2006

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Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
255	Propylene glycol/TPGS/Capmul MCM NF (5:5:2 by weight)	Dog	PO	13-weeks	5 mL/kg BID	Administration of the vehicle was associated with emesis and abnormal fecal quality throughout the 13 weeks of the study	Beagle dogs (Marshall) age ~6 months at study initiation; ♂/♀	New contributed data
256	PVP K30 (10%)/sodium citrate buffer (50 mmol/L, pH 5)	Rat	PO (gavage)	1 day	10 mL/kg SD	None	Age 6 weeks; ♂/♀	New contributed data
257	PVP K30 (10%)/sodium citrate buffer (50 mmol/L, pH 5)	Nonhuman primate	PO (gavage)	4 weeks	5 mL/kg once weekly	None	Age 5-7 years; ♂/♀	New contributed data
258	PVP K30 (10%)/sodium citrate buffer (50 mmol/L, pH 5)	Nonhuman primate	PO (gavage)	28 days	5 mL/kg QD	None	Age 2-3 years; ♂/♀	New contributed data
259	Sesame oil/EtOH (96/4)	Dog	PO	28 days	2 mL/kg	Well tolerated		Contributed data, 2006
260	Sesame oil/EtOH (96/4)	Rat	PO	28 days	2 mL/kg	Well tolerated		Contributed data, 2006
261	Sodium acetate (25 mmol/L, USP)/ lactose (70 mg/mL)/water (sterile for injection, USP, pH 4.5)	Dog	SC	14 doses	1 mL/kg	Red discoloration and swelling at injection sites; chronic active inflammation and hemorrhage		Contributed data, 2006
262	Sodium acetate (25 mmol/L, USP)/ lactose (70 mg/mL)/water (sterile for injection, USP, pH 4.5)	Rat	SC	14 doses	10 mL/kg	Scabbing at injection site		Contributed data, 2006
263	Sodium acetate (25 mmol/L, USP)/ lactose (70 mg/mL)/water (sterile for injection, USP, pH 4.5)	Rat	SC	14 doses	4 mL/kg	None		Contributed data, 2006
264	Sodium acetate (USP, 25 mmol/L)/ lactose (USP/EP, 70 mg/mL)/water (pH 4.5)	Rat	SC	28 days	10 mL/kg	Well tolerated		Contributed data, 2006
265	Sodium acetate in NaCl, 5 mmol/L	Rat	IV	1 month	1 mL/kg	Well tolerated		Contributed data, 2006
266	Sodium acetate trihydrate buffer (50 mmol/L)/Tween 80 (1%)	Mouse	PO (gavage)	26 weeks	10 mL/kg/d	Well tolerated		Contributed data, 2006
267	Sodium acetate trihydrate buffer (50 mmol/L)/Tween 80 (1%)	Mouse	PO (gavage)	7 days	10 mL/kg/d	Well tolerated		Contributed data, 2006
268	Sodium citrate/NaCl buffer	Rat	IV	2 weeks	4 mL/kg bolus, 2/10 minutes	Well tolerated		Contributed data, 2006
269	Sodium CMC (0.1%)/methylparaben sodium (0.1%)/propylparaben sodium (0.02%)/water (purified; wt/vol)	Mouse	PO (gavage)	105 weeks	10 mL/kg/dose BID	None	Age 7 weeks; ♂/♀	New contributed data
270	Sodium CMC (0.1%)/methylparaben sodium (0.1%)/propylparaben sodium (0.02%)/water (purified; wt/vol)	Rat	PO (gavage)	104 weeks	10 mL/kg/dose BID	None	Age 6 weeks; ♂/♀	New contributed data

(continued)

Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
271	Sodium hydroxide (0.1 mol/L)/NaCl for injection, USP (0.9%)	Nonhuman primate	IV (30-minute infusion)	14 days	10 mL/kg QD	None	Age 2-4.5 years; ♂/♀	New contributed data
272	Sodium hydroxide (10% solution): 2%/phenoxyethanol: 1%/Carbomer 974P NF: 1%/in purified water	Mouse	Topical	28 days	3.4 mL/kg QD	None	GLP; age 7 weeks; 12♂/12♀	New contributed data
273	Sodium phosphate (10 mmol/L)/NaCl (0.8%)/Tween 20 (0.05%)/water (sterile for injection, USP, pH 6.0 ± 0.3)	Rat	SC	26 weeks	1,500 µL/kg twice weekly	None	Age 6 weeks; ♂/♀	New contributed data
274	Sodium phosphate (20 mmol/L)/ sucrose (1%)/mannitol (4%)/water (for injection)	Rat	SC	26 weeks	1.38 mL/kg QD	None	Age 7 weeks; ♂/♀	New contributed data
275	Sodium phosphate (20 mmol/L)/ sucrose (1%)/mannitol (4%)/water (for injection)	Rabbit	SC	39 weeks	0.58 mL/kg QD	None	Age 5-6 months; ♂/♀	New contributed data
276	Sodium phosphate buffer (0.3 mol/L)/ PEG 400, pH 8 (70:30, wt/wt)	Nonhuman primate	PO (gavage)	4 weeks	2 mL/kg/d (0.4 mL/ min/kg)	Well tolerated		Contributed data, 2006
277	Sodium phosphate buffer (20 mmol/ L)/dextrose (4%)/sodium hydroxide (pH 7.9-8.1)	Rat	Infusion	4 days	2 mL/kg/h	None	Age 8 weeks; ♀	New contributed data
278	Sodium succinate (25 mmol/L)/ lactose (45 mg/mL)/NaCl (0.45%)/ water (sterile for injection, USP)	Dog	IV	7 doses	1 mL/kg	None		Contributed data, 2006
279	Sodium succinate (25 mmol/L)/ lactose (45 mg/mL)/NaCl (0.45%)/ water (sterile for injection, USP)	Dog	SC	14 doses	1 mL/kg	None		Contributed data, 2006
280	Sodium succinate (25 mmol/L)/ lactose (45 mg/mL)/NaCl (0.45%)/ water (sterile for injection, USP)	Rat	IV	7 doses	1 mL/kg	None		Contributed data, 2006
281	Sodium succinate (25 mmol/L)/ lactose (45 mg/mL)/NaCl (0.45%)/ water (sterile for injection, USP)	Rat	SC	14 doses	1 mL/kg	None		Contributed data, 2006
282	Sodium succinate (25 mmol/L)/ mannitol (250 mmol/L)/water (sterile for injection, pH 4.6)	Rat	SC	SD	4 mL/kg	None		Contributed data, 2006
283	Solutol HS 15/EtOH/Water (40/10/ 50, vol/vol/vol)	Dog	PO	q7d over 8 weeks	1.5 mL/kg	None	Non-GLP; age 1-4 years; 3♂/3♀	New contributed data
284	Solutol HS 15: 15%/EtOH: 5%/PBS	Dog	PO	5 days	20 mL/kg QD	May cause vomiting, loose stool	Non-GLP; age 1-2 years; 2♂	New contributed data
285	Solutol: 10%/in NaCl	Rat	IV	14 days	6 mL/kg SD	None	Non-GLP; age 10 weeks; 3♂/3♀	New contributed data

(continued)

Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
286	Solutol HS15/EtOH/water (40/10/50)	Nonhuman primate	PO (gavage)	9 months	3 mL/kg/d	Well tolerated		Contributed data, 2006
287	Sorbitol (5%)/histidine (10 mmol/L)/ Tween 80 (0.01%)/water (sterile for injection, USP, pH 5.8)	Dog	IV (bolus)	5 weeks	4.98 mL/kg once weekly	None	Age 2-3 years; ♂/♀	New contributed data
288	Soybean oil: 50.00%/coconut oil: 23.60%/mineral oil: 5.80%/ cyclomethicone: 5.00%/cetostearyl alcohol: 3.50%/stearic acid: 3.00%/ myristyl alcohol: 2.50%/ hydrogenated castor oil: 2.00%/white wax (beeswax): 2.00%/stearyl alcohol: 1.50%/docosanol: 1.10%	Minipig	Topical	3 weeks	0.25 mL/kg QD	None	GLP; age 3-4 months; 5♂/5♀	New contributed data
289	Sucrose (1%)/NaCl (100 mmol/L)/L-arginine hydrochloride (25 mmol/L)/ sodium phosphate (25 mmol/L, pH 6.3)/water (for injection, USP)	Nonhuman primate	SC	4 weeks	2 mL/kg twice weekly	Soft/watery feces	Age 2.5-3.5 years; ♂/♀	New contributed data
290	Sucrose acetate isobutyrate/EtOH/ PEG 300 (90/5/5)	Cat	Oral mucosa	8 hours	0.1 mL SD	None	Non-GLP; age >6 months; 3♀	New contributed data
291	TPGS (2%)/HPMC acetate succinate (1% HF grade)/PVP K30 (0.25%)/ water (DI)	Rat	PO (gavage)	91 days	10 mL/kg QD	None	Age 6 weeks; ♂/♀	New contributed data
292	TPGS (2%)/HPMC acetate succinate (1% HF grade)/PVP K30 (0.25%)/ water (DI)	Dog	PO (gavage)	91 days	10 mL/kg QD	None	Age 6-7 months; ♂/♀	New contributed data
293	TPGS (2%)/HPMC acetate succinate (1% HF grade)/PVP K30 (0.25%)/ water (DI)	Rabbit	PO (gavage)	14 days	10 mL/kg QD	None	Age 5-8 months; ♂/♀	New contributed data
294	TPGS (2%)/HPMC acetate succinate (1.5% HF grade)/PVP VA 64 (1.5%)/ sodium citrate (50 mmol/L pH 5)/ water (DI)	Rat	PO (gavage)	28 days	10 mL/kg QD	None	Age 6-8 weeks; ♂/♀	New contributed data
295	TPGS (5%)/methylcellulose 400 cP (0.5%)/water (DI)	Rat	PO (gavage)	1 day	10 mL/kg SD	None	Age 6 weeks; ♂/♀	New contributed data
296	Trehalose (9%)/lactic acid (10 mmol/ L)	Dog	IA	q28d × 4 doses over 85 days	0.4 mL	None	GLP; age 9-11 months; 5♂/5♀	New contributed data
297	Trehalose (9%)/lactic acid (10 mmol/ L)	Dog	IV	2×/wk × 8 doses over 28 days	0.5 mL/kg	None	GLP; age 1 year; 3♀	New contributed data
298	Trehalose (9%)/lactic acid (10 mmol/ L)	Rat	IV	14 days	0.5-5 mL/kg SD	None	GLP; age 16-20 weeks; 6♂/6♀	New contributed data
299	Tween 20 (0.01%)/sodium acetate (10 mmol/L)/sorbitol (5%, pH 5)	Nonhuman primate	IV (bolus)	12 weeks	5 mL/kg once weekly	None	Age 2-4 years; ♂/♀	New contributed data

(continued)

Table 114 (continued)

No.	Formulation	Species	Route	Duration	Dose	Adverse reactions/toxicity	Notes	Data source
300	Tween 20 (0.01%)/sodium acetate (10 mmol/L)/sorbitol (5%, pH 5)	Rat	IV (bolus)	12 weeks	5 mL/kg once weekly	None	Age 7 weeks; ♂/♀	New contributed data
301	Tween 80/CMC/dimethicone (0.01%; ratio PS80/CMC of 1:1, 0.2% PS80 and CMC)	Rabbit	PO (gavage)	1 month	3 mL/kg/d	Well tolerated		Contributed data, 2006
302	Tween 80 (10%)/citric acid (10.5 mg/mL)/water (sterile solution)	Rat	IV	2 doses	3 mL/kg	None		Contributed data, 2006
303	Vitamin E (20%)/sodium citrate buffer (50 mmol/L, pH 5)	Rat	PO (gavage)	28 days	10 mL/kg QD	None	Age 8 weeks; ♂/♀	New contributed data
304	Water (sterile for injection, USP)/ sodium hydroxide	Rat	SC	SD	1 mL/kg	Necrosis of the subcutaneous muscle panniculus carnosus, inflamed injection		Contributed data, 2006
305	Xanthan gum NF (also known as: Xantural 180; 0.2%, wt/vol)/Tween 80 NF (0.255%, wt/vol)/water (sterile for injection, USP)	Rat	PO (gavage)	5 days	10 mL/kg/dose BID	None	Age 8-10 weeks; ♀	New contributed data

Abbreviations: ADME, absorption, distribution, metabolism, excretion; AST, aspartate transaminase; BHA, butylated hydroxyanisole; BID, twice a day; BHT, butylated hydroxytoluene; CMC, carboxymethylcellulose; DAM, diacetylmonoxime; DI, deionized; DMA, dimethyl acetamide; DMSO, dimethylsulfoxide; EDTA, ethylenediaminetetraacetic acid; EOD, every other day; EP, European Pharmacopeia; EtOH, ethanol; GLP, good laboratory practice; HF, hydrofluoric acid; HPβCD, hydroxypropyl-β-cyclodextrin; HPMC, hydroxypropyl methylcellulose; IA, intra-articular; IM, intramuscular; IP, intraperitoneal; IV, intravenous; LD_{50}, lethal dose for 50% of population; MTD, maximum tolerated dose; NF, National Formulary; NMP, *N*-methyl-2-pyrrolidone; NOEL, no adverse effect level; PBS, phosphate-buffered saline; PEG, polyethylene glycol; PET, polyethylene terephthalate; PO, oral; PVP, polyvinylpyrrolidone; QD, once a day; q7d, every 7 hours; q30d, every 30 hours; q1h, every 1 hour; RBC, red blood cell; SC, subcutaneous; SD, single dose; TID, 3 times a day; TPGS, D-α-tocopheryl polyethylene glycol succinate; USP, United States Pharmacopoeia; VA, vinyl acetate.

Author Contributions

S. Gad contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; and critically revised the manuscript. L. Eagle contributed to design and drafted the manuscript. C. Spainhour contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; and critically revised the manuscript. C. Shoemake, D. R. Stackhouse Pallman, A. Stricker-Krongrad, P. Downing, R. Seals, K. Polhamus, and J. Daly contributed to acquisition, analysis, and interpretation, and drafted the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

Authors' Note

Gad Consulting Services maintains files and copies of all the source data and references and will endeavor to answer all reasonable queries and provide access to researchers.

Declaration of Conflicting Interests

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