IMIDOCARB DIPROPIONATE

First draft prepared by
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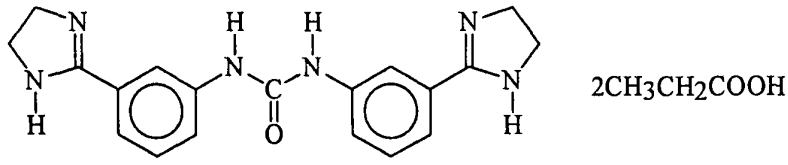
IDENTITY

Chemical name: N,N'-bis[3-(4,5-dihydro-1H-imidazol-2-yl)phenylurea dipropionate

Synonyms: Imizol; 4A65; BW4A65; HR-2073; IMDP

Structural formula:



$2CH_3CH_2COOH$

CAS number: 27885-92-3 (imidocarb)

Molecular formula: $C_{25}H_{32}N_6O_5$

Molecular weight: 496.55

OTHER INFORMATION ON IDENTITY AND PROPERTIES

Pure active ingredient: Imidocarb (purity not specified).

Appearance: Off-white to pale cream powder.

Melting point: 254°C (Sponsor); 350°C (as hydrochloride salt, Merck Index)

Solubility: Soluble in water (74% m/V) and methanol; moderately soluble in acids; slightly soluble in buffer at pH 7.8; practically insoluble in base; insoluble in non-polar organic solvents, such as acetone.

Optical rotation: Optically inactive.

Ultraviolet maxima: Not reported.

RESIDUES IN FOOD AND THEIR EVALUATION

CONDITIONS OF USE

General

Imidocarb has been approved in a number of countries since the early 1970's for the treatment of the protozoal diseases babesiosis (in cattle and sheep) and anaplasmosis (in cattle). Currently, it is used in Africa and the mid-East, Europe and South America for the treatment of these diseases, which are transmitted by ticks. The typical commercial

formulation is an injectable solution of 12% m/V imidocarb dipropionate in water buffered to pH 4.5 with propionic acid.

Dosage

The typical dosage for cattle is a single treatment of 1.2 to 3.0 mg/kg BW imidocarb dipropionate, which may be repeated at 4 week intervals for prophylaxis of babesiosis. A single dose of 1.2 mg/kg BW imidocarb dipropionate is recommended for sheep, with a second dose 2 weeks later, if required. The formulated product may be injected either by intramuscular (IM) or subcutaneous (SC) injection, with SC being the preferred route of administration.

PHARMACOKINETICS AND METABOLISM

Pharmacokinetics

Toxicological Test Species

Rats

Rats administered orally with ^{14}C-imidocarb dihydrochloride were killed at 2, 6 or 24 hours after dosing (Farebrother, 1973). In the same study, other rats dosed orally with ^{14}C-imidocarb dipropionate were killed at 48 hours after exposure, while rats treated subcutaneously with the dihydrochloride were sacrificed 7 days following dosing. Wholebody autoradiography, after sacrifice of the rats killed at 2 or 6 hours, showed activity outside the gut only in liver and kidney, with slight traces of radioactivity remaining in these organ tissues at 24 hours. In the rats killed 48 hours after oral treatment with ^{14}C-imidocarb propionate, traces of radioactivity were found in kidney tissue. In the rats killed at 7 days after treatment, high activity remained at the injection site, with radioactivity also detectable in skeletal muscle (higher near the injection site) and traces in kidney and liver. The results demonstrated poor absorption of imidocarb from the gut following oral administration, with more effective distribution resulting from the subcutaneous injection.

In the first of two studies using unlabelled imidocarb (Nimmo-Smith, 1968), a variety of doses and routes of administration were used, with the salt form of imidocarb not specified. Following SC injection at 10 mg/kg BW, only about 19% of the dose as parent compound was excreted within 78 hours, with three-quarters of this in the urine. Following multiple doses administered by the oral or intraperitoneal routes, highest tissue residues were found in kidney, with significant residues also found in liver. In rats treated by a single SC injection of 5 mg/kg BW and killed at varying time periods up to 56 days following treatment, residues in kidney and liver were found to have an initial half-life of about 3 days, increasing after the initial 3 days to 7-8 days. There was indication of significant tissue binding in liver. In the second of these studies (Thomson, 1975), female Wistar rats were administered imidocarb dipropionate at 5 mg/kg BW by stomach tube, either using a single treatment or once daily for 30 days. Rats were sacrificed 24 hours after final exposure and tissues were assayed by an unspecified analytical method. Residues in kidneys were approximately 10 mg/kg, while residues in liver were in the range of 1-2 mg/kg and in muscle <0.5 mg/kg, for animals which received both the single and multiple doses.

Mice

Two studies were reported in which mice received 1 mg/kg BW ^{14}C-imidocarb dihydrochloride by intravenous (IV) injection (Anonymous, 1968a, b). In the first of these studies, excretion was rapid, with residues observed in urine within 5 minutes of dosing. Within 96 hours, about 90% of the drug was excreted (56-65% in urine, 23-25% in faeces). In mice killed at 5 minutes or 8 hours after dosing, residues in liver were constant at 33% of the dose, while in kidneys residues diminished from 27% of dose to 6%. At 96 hours, 2.8% of the dose was found in liver and 0.6% in kidneys. In the second study, mice were sacrificed at 3.5 hours after IV injection, with 29% of the dose found in liver and 6.8% in kidney. Within 2 hours of dosing, 37% of the drug was excreted in urine and 95% of the radioactivity co-eluted with imidocarb in three different paper chromatography separation systems. Over 90% of the residues extracted from liver and kidney also co-chromatographed with parent imidocarb, indicating little metabolic conversion of the parent compound.

Dogs

In male beagle dogs, administered 5 mg/kg BW imidocarb (free base basis) dipropionate once daily by gavage for 30 days and killed at 24 hours after final treatment (Chesher *et al*, 1976), highest residues were found in liver (98 ± 37 mg/kg), followed by kidneys (7.3 ± 2.1 mg/kg) and muscle (<0.5 mg/kg). In mongrel dogs which received an

intravenous bolus dose of 4 mg/kg imidocarb dipropionate, the plasma half-life $t_{½}$ was reported as 207 ± 45 min, with approximately 80% of the dose eliminated within 8 h of treatment (Abdullah and Baggot, 1983).

Monkeys

In 5 female monkeys dosed orally once daily for 30 days with 5 mg/kg BW imidocarb dipropionate, residues in tissues collected at slaughter (time following final dose not stated) were 1.02 ± 0.23 mg/kg in liver, 1.07 ± 0.62 mg/kg in kidney and <0.5 mg/kg in muscle (Thompson, 1975b).

Metabolism in Food Animals

Cattle

In a preliminary study comprising three reports (Nimmo-Smith and Savage, 1973; Chesher *et al*, 1973; Chesher and Malone, 1973), 2 lactating and 4 non-lactating cows were administered 6 mg/kg BW ^{14}C-imidocarb dipropionate by intramuscular (IM) injection twice, with 14 days between the injections. Maximum concentrations in plasma were achieved within 30 minutes and initial excretion, primarily in urine, was rapid. The plasma half-life lengthened with time following treatment, being 45-55 days by 60 days after the second dose. Less than half the dose was excreted in the first week following treatment, with elimination also slowing with increasing time. Maximum residues were found in milk within 24 hours of treatment, with the terminal half-life in milk being about 15 days. Total residues were highest in injection sites, followed by liver, kidney and muscle. This work was not conducted to GLP standards.

Subsequently, a non-GLP study was conducted in which 9 calves each received 0.5 mg/kg BW imidocarb dipropionate by IV injection, following which blood samples were collected at 5, 15, 30 and 60 min, and at 2, 4, 8, 16 and 24 h (Nimmo-Smith and Savage, 1974; Chesher *et al*, 1974). The calves were subsequently killed in groups of 3 at 7, 30 and 60 days after administration of the drug. The experiment was repeated with another 9 calves which received imidocarb dipropionate as a pour-on mixture applied as a 5% solution to provide a dose of 30 mg/kg BW, with blood samples collected at 2, 4, 8, 16 and 24 h and at 2, 4 and 7 days post-dosing. Animals were killed on the same schedule as the calves which received imidocarb intravenously. In addition, 5 heifers received imidocarb dipropionate at 3 mg/kg BW by IM injection in the gluteal muscle and were killed at 172 days following treatment. After the IV dosing, plasma half-life over the first hour was 24 min, increasing to 3.2 h over the next 7 h and to 7.5 h from hours 8-24. Drug concentrations in plasma achieved a concentration of 2.2 mg/L at 5 min after treatment, declining to 0.75 mg/L at 1 h and to 0.02 mg/L at 24 h By comparison, dermal treatment resulted in a mean concentration of imidocarb in plasma of 0.01 mg/L at 2 h after dosing, with the maximum mean value achieved being 0.10 mg/L at 16 h. The highest individual result was 0.17 mg/L in one animal at 2 days following exposure, with a greater variability in imidocarb concentrations in plasma evident for the dermal exposure, but with an overall greater persistence.

The following concentrations of imidocarb were found in animals killed following IV dosing: day 7 - liver, 4.62-6.89 mg/kg; kidney, 6.01-24.9 mg/kg; muscle, not tested; day 30 - liver, 1.75-3.59 mg/kg; kidney, 3.26-4.55 mg/kg; muscle, not tested; day 60 - liver, 0.68-3.29 mg/kg; kidney, 1.63-3.13 mg/kg; muscle, 0.16-0.30 mg/kg. Following dermal exposure, residues were as follows: day 7 - liver, 1.60-4.75 mg/kg; kidney, 25.5-45.3 mg/kg; muscle, not tested; day 30 - liver, 1.84-3.00 mg/kg; kidney, 1.07-2.63 mg/kg; muscle, not tested; day 60 - liver, 1.29-1.52 mg/kg; kidney, 1.74-4.49 mg/kg; and muscle, 0.23-0.32 mg/kg. In the 5 heifers slaughtered 172 days following IM injection with 3 mg/kg BW imidocarb dipropionate, residues were detected as follows: liver, 1.11 ± 0.55 mg/kg; kidney, 4.18 ± 3.05 mg/kg; muscle, 0.13 ± 0.04; and fat, 0.04 ± 0.03 mg/kg. The results indicated considerable differences in residues in individual animals and no statistically significant differences in residue levels in tissues, with the possible exception of kidney at 30 days (P=0.05), when residues resulting from IV dosing and dermal exposure were compared. In this study, plasma and tissue samples were analyzed first by a colourimetric method with a claimed limit of detection of 0.1 mg/kg (Nimmo-Smith and Ince, 1969) and, where greater test sensitivity was required, were subsequently analyzed by a fluorometric method (Nimmo-Smith and Norton, 1973).

A more recent study (Ferguson, 1996) was reported in which dairy cows and male and female calves were treated with a single SC dose at 3 mg/kg BW of ^{14}C-imidocarb dipropionate formulated as Imizol. Peak concentrations of 1.32 ± 0.44 mg equivalents/kg of ^{14}C-imidocarb were found in blood at 1 h post-treatment, remaining constant to 4 h, and then declining to <0.05 mg/kg by 3 days after treatment. In blood samples collected at 1, 6, 14 and 36 hours post-dosing, from 72.0 to 90.9% of the radioactivity recovered was protein bound, with no difference found at the various collection times. Excreta were collected for 28 days following treatment, with 58.52 ± 5.23% of the drug recovered, the majority (38.65 ± 4.63%) in faeces and the remainder (15.31 ± 3.20%) in urine. Most of the recovered radioactivity in urine was parent compound, but some faecal samples contained a significant amount of an unidentified metabolite (day 4, 27.86%; day 10, 13.22%).

In dairy cows slaughtered 28 days post-dosing and in calves killed at 56 and 90 days post-dosing, 77.72 ± 5.98% to 83.58 ± 4.94 % of the total radioactive residue in liver was recovered, of which 83 - 84% co-chromatographed with imidocarb by HPLC. The remaining recovered residue was contained in a smaller, unidentified chromatographic peak, which was also seen in other matrices. TLC analysis gave similar results. The minor peak observed in the day 28 samples was also seen in liver samples in the day 56 and day 90 groups. Over 90% of the total radioactive residue in kidneys was extractable in the day 28, 56 and 90 samples, with 80% or more of this matching imidocarb parent compound in HPLC (>90% at days 56 and 90). In muscle, 79.7% of total radioactive residues was recovered by extraction from the dairy cattle (day 28), with 90.6% recovered from day 56 samples and 96.0% from day 90 samples. Most of this was associated with parent compound in all muscle samples. An unidentified peak which accounted for 9.06 ± 4.98% of the total residues in liver in the day 28 samples was also present in the liver samples for days 56 and 90 and in all kidney samples. This compound, also found in faecal samples, was not detected in any muscle samples. In milk, 77.1 to 95.1% of total radioactivity was extracted, with the recovery increasing with time from dosing, and >70% of this being parent compound through day 3 samples. On day six 36% of the recovered radioactivity was parent compound and, due to the low level of radioactivity recovered from subsequent samples, no assignment was made. The day 1 sample was the only one to contain a second compound, which accounted for 2.19% of the total radioactivity.

In another recent study (Coldham *et al*, 1995), no metabolism was seen for imidocarb in *in vitro* studies with bovine liver. Following a single SC injection of 3 mg/kg BW imidocarb dipropionate in cattle also reported in this study, depletion of imidocarb in tissues followed a two compartment model, with α- and β-phase halflives of 31.7 and 48.5 days in liver and 34.9 and 120.7 days in muscle, respectively.

Sheep

In a series of non-GLP experiments in which sheep were dosed with imidocarb dipropionate, two sheep killed 24 h after treatment with 50 μg/kg BW of ^{14}C-imidocarb had residues distributed throughout the central nervous system (Aliu *et al*, 1977). In three sheep which received 2.0 mg/kg BW imidocarb dipropionate intravenously, concentrations of imidocarb in plasma declined rapidly in the first hour from 10.8 μg/mL to 1.9 μg/mL and to <1 μg/mL over the next 4 h. Imidocarb dipropionate administered by IM injection (4.5 mg/kg BW) to 7 sheep gave peak concentrations in plasma of 7.9 μg/mL within 4 h, decreasing to 4.6 μg/mL at 6 h. Subsequent reduction of residues was slow, following first-order kinetics, with detectable residues in plasma 4 weeks after treatment. As in studies with cattle, significant protein binding was observed. Initial urinary excretion rates were high (14.5% in first 24 h), but reduced rapidly (1.14% in second 24 h). Concentrations of imidocarb in the bile exceeded those found in plasma. No metabolites were found by TLC analysis of urine, bile, liver or kidney samples. Highest tissue residues were found in kidneys of 5 sheep slaughtered at 4, 6, and 24 h and 32 days, respectively after treatment with a single IM dose of 4.5 mg/kg BW imidocarb (2 sheep killed at 24 h, 1 only at other times). Residue concentrations were lower in liver, followed by fat and muscle. Imidocarb residues in milk of lactating ewes peaked at 12 hours post-dosing, decreasing slowly at about the same rate as residues in plasma.

TISSUE RESIDUE DEPLETION STUDIES

Radiolabeled Residue Depletion Studies

Cattle

Total residues in tissues resulting from treatment of dairy cows and male and female calves with a single SC dose at 3 mg/kg BW of ^{14}C-imidocarb dipropionate formulated as Imizol (Ferguson, 1996) are reported in Table 1. In injection sites, mean residue values were as follows: day 28, 1.73 ± 1.20 mg/kg; day 56, 1.35 ± 1.70 mg/kg; day 90, 0.54 ± 0.30 mg/kg. Samples were analyzed initially by combustion to determine total ^{14}C-residues. Subsequently, total extractable residues, extracted into acetonitrile, followed by extraction at acid and basic pH's, were determined. The extractable residues were analyzed by liquid chromatography, with radiometric detection, to determine the amount of parent compound present in the extract. This measurement was undertaken for kidney and liver samples from each animal, as well as for pooled muscle and milk samples, for each time point. The determination was not made for fat, due to the relatively low amounts of residue found in that tissue. Furthermore, it should be noted that this extraction did not include the treatment with protease to release bound residues, which is included in the proposed regulatory method. These data, however, permit an estimation of the marker residue as a percentage of the total residue at the various time points included in the study.

Based on the data in Table 1, parent compound comprises, on average, 68% of the total ^{14}C-imidocarb residues found in liver at the various time points, 88% of the residue in muscle and kidney and 77% of the residue found in milk. There is no indication from the data that the proportion of the parent compound to total residues found in tissues or milk changes with time from treatment. In the case of milk, the data for the sample collected at 6 days were not included in the calculation of the average as the measurements were essentially at the detection limit and therefore were not considered as quantitatively reliable. They are included in the table, however, to demonstrate the elimination of residues from milk at 6 days post-treatment.

Table 1. Total residues and residues of parent compound found in tissues and milk of dairy cattle[1] and calves[2] which received a single SC dose (3 mg/kg BW) of ^{14}C-imidocarb dipropionate.

Sample	Day	Total ^{14}C-Residue (mg/kg)	% Total Residue Extractable	^{14}C- Imidocarb Residue as Parent (mg/kg)	Parent as % of Total Residue
Liver	28	8.24±4.07	78	5.34±2.35	66
	56	4.01±0.42	84	2.79±0.45	70
	90	2.19±0.83	81	1.51±0.76	67
Kidney	28	12.81±4.65	95	10.59±4.36	82
	56	3.77±0.93	95	3.44±0.64	92
	90	1.40±0.49	92	1.27±0.46	91
Muscle	28	0.68±0.80	80	0.54[a]	79
	56	0.41±0.22	91	0.37[a]	89
	90	0.31±0.18	96	0.30[a]	95
Fat	28	0.13±0.07	---	---	---
	56	0.10±0.02	---	---	---
	90	0.03±0.02	---	---	---
Milk	1	0.37±0.22	77	0.26[a]	70
	2	0.19±0.05	80	0.15[a]	79
	3	0.10±0.04	86	0.07[a]	73
	6	0.03±0.01	95	0.01[a]	36

[1] Treated animals were mature dairy cattle, weight range 470 to 575 kg on receipt (n = 6).
[2] Treated animals were calves, weight range 118 to 158 kg on receipt (n = 4 per group).
[a] Analysis of pooled samples.
--- Not analyzed.

Other Residue Depletion Studies (with Unlabelled Drug)

Cattle

In a study conducted to GLP standards, forty calves were administered a single SC dose of 3 mg/kg BW imidocarb dipropionate and slaughtered in groups of four at 14, 28, 42, 56, 70, 98, 140, 168, 196 and 224 days post-treatment (Gaffney, 1992). Muscle samples were initially analyzed by an HPLC method with a claimed limit of determination of 0.025 mg/kg and recovery of 68.7 ± 7.9%. Subsequently, muscle and liver samples were apparently analyzed by an HPLC method with a claimed limit of determination of 0.01 mg/kg and recovery of 90 ± 3% in muscle and, for liver, a limit of detection of 0.07 mg/kg and recoveries of 64 ± 4% (Coldham *et al*, 1995). Kidney, fat and injection site samples were also collected, but no analytical results were reported. Results of the muscle and liver analyses are given in Table 2. Analytical results reported for muscle in the second report (Coldham *et al*, 1995), differ slightly from those reported in the original research document, but the analytical conditions reported in this reference suggest that the samples were re-analyzed for the published paper. The elapsed period from sample collection to analyses as reported in this paper was not stated, so the reliability of using these results to predict residues in freshly collected tissue may be questioned.

Two older studies were also reported in which tissue residues were measured in cattle treated with imidocarb, but these studies were not to GLP standards. In the first study, the results of which are contained in two reports (Crawley and Thomas, 1981; Taylor *et al*, 1981), cattle were treated by IM injection with 1 or 2 doses of 3 mg/kg BW imidocarb dipropionate. Cattle which received the single dose were killed, in groups of four (3 treated, 1 control), at 7, 14 and 28 days post-dosing. Cattle, which received a second dose 28 days after the first dose, were slaughtered at 14, 28 and 42 days after the second dose. Liver, kidney, muscle, fat and injection sites were collected from all animals and analyzed by a colourimetric method of analysis (Nimmo-Smith and Ince, 1969). Residues found in tissues from the animals in this study are reported in Table 3.

Table 2. Residues of imidocarb in muscle and liver of calves dosed with a single SC injection of imidocarb dipropionate at 3 mg/kg BW (results corrected for recovery)

Days after dosing	Imidocarb residues in tissue (mg/kg), n = 4			Days after dosing	Imidocarb residues in tissue (mg/kg), n = 4		
	muscle[1]	muscle[2]	liver[2]		muscle[1]	muscle[2]	liver[2]
14	1.07 ± 0.39	1.05 ± 0.31	5.4 ± 0.61	98	0.21 ± 0.03		
28	0.38 ± 0.09			140	0.15 ± 0.05		
42	0.40 ± 0.09			168	0.10 ± 0.03		
56	0.37 ± 0.08			196	0.12 ± 0.02		
70	0.31 ± 0.11			224	0.06 ± 0.01	0.06 ± 0.02	0.12 ± 0.01

[1] Results as per Gaffney, 1992; [2] Results as per Coldham *et al*, 1995.

Table 3. Residues of imidocarb resulting from IM injection (1 or 2 doses) of 3 mg/kg BW imidocarb dipropionate in cattle

Withdrawal Time (days)	Number of injections	Range of Imidocarb Residues in Tissues, mg/kg (n=3)					
		Liver	Kidney	Muscle	Fat[1] (omental)	Initial Injection Site	Second Injection Site
7	1	13.6 - 19.8	9.0 - 20.1	0.5 - 2.2	<0.1	3.8 - 4.4	
14	1	7.3 - 11.0	8.4 - 10.7	0.5 - 2.1	0.2 - 0.4	1.5 - 3.4	
14	2	6.9 - 19.5	13.9 - 26.2	2.0 - 3.6	0.4	2.1 - 3.1	2.1 - 8.2
28	1	2.4 - 4.8	2.3 - 3.1	<0.1 - 0.8	<0.1	1.0 - 2.8	
28	2	8.9 - 21.3	15.1 - 22.9	1.0 - 1.9	0.4	1.1 - 2.5	1.6 - 2.6
42[2]	2	5.4, 8.2	6.5, 15.1	0.4, 0.8	0.3, 0.3	1.0, 1.6	0.6, 1.1

[1] Perirenal fat was also analyzed, but residues (0.1 mg/kg) were only found in one sample from one animal at each of days 7 and 14;
[2] Only two animals slaughtered in this group. (1), (2) indicates initial and second injection sites.

In the remaining study (Piercy and Malone, 1976), the persistence of imidocarb at intramuscular and subcutaneous injection sites in male calves which received 5 mg/kg BW imidocarb dipropionate w. , determined at 30 days following administration using the same colourimetric method as in the preceding study. Residues ranged from 3.46 - 5.35 mg/kg in the SC injection sites and from 1.75 - 3.90 mg/kg in the IM injection sites. There was little difference in the total residues found at the injection site for either type of administration (total residue 0.59 ± 0.09 mg for SC sites; total residue 0.64 ± 0.18 for IM sites).

Two studies were conducted to determine the depletion of imidocarb in milk, again not to GLP requirements. In the first of these studies, detailed in four reports (Crawley, 1982a; Crawley, 1982b; Taylor and Mountford, 1981; Taylor, 1981), 3 cows received a single dose of 3 mg/kg BW imidocarb dipropionate (Crawley, 1982a), which was repeated 28 days later (Crawley, 1982b). Samples were initially analyzed by a gas chromatographic method using alkali flame

detection (Taylor, 1981), but were subsequently analyzed by gas chromatography/mass spectrometry (GC/MS), with a limit of detection of 0.01 mg/L (Crawley, 1982a,b). Residue depletion results are given in Table 4.

In the second study, detailed in two reports (Crawley and Swallow, 1983; Woollon, 1983), 4 cows were treated in a crossover dosing regimen, repeated after 35 days, in which they received 3 mg/kg BW imidocarb dipropionate IM either in the cervical or gluteal musculature. Milk samples were collected for 8 days following treatment and analyzed as by gas chromatography/mass spectrometry (Crawley, 1982b). Peak residue levels were in samples collected 24 h following treatment (IM in cervical musculature, 0.38-0.73 mg/L; IM in gluteal musculature, 0.28-0.86 mg/L), declining by approx. 50% by day 2 and to 0.02 mg/L or less after 8 days. The depletion profile was similar for injection in either muscle site and consistent with results observed in a recent study where ^{14}C-imidocarb dipropionate was administered SC at 3 mg/kg BW (Ferguson, 1996).

Table 4. Depletion of imidocarb in milk following IM dosing of lactating cattle with 3 mg/kg BW imidocarb dipropionate (1 or 2 treatments, 28 days apart), as measured by GC/MS.

Time Post-Dose (Days)	Range of Imidocarb Residue Concentration, mg/L[a] (n=3)	Time Post-Dose (Days)	Range of Imidocarb Residue Concentration, mg/L[a] (n=3)
0.5	0.30 - 0.66	21	<0.01
1.0	0.60 - 0.79	28	<0.01
2	0.20 -0.55	29 (2nd dose after day 28 sample)	0.35, 0.52[1]
3	0.07 - 0 23	30	0.11[2]
7	<0.01	31	0.07 - 0.30
14	<0.01	38	<0.01, 0.10[1]

[a] Results are mean values for milk from each animal
[1] Samples available from only 2 of 3 animals.
[2] Sample available from only 1 of 3 animals.

Sheep

In a non-GLP study, twelve female sheep received two IM injections at 1.2 mg/kg BW imidocarb dipropionate, with a 7-day interval between injections. Groups of 3 sheep were killed at 7, 14, 28 and 56 days after the second treatment. In addition, 3 sheep were injected only with water and slaughtered 28 days later to provide controls (Woollon and James, 1983). However, analytical results were reported only for tissues from the sheep killed at 7, 14 and 28 days after the second treatment (Crawley, 1983; McHardy *et al*, 1986). As in several other studies, the colourimetric method of analysis (Nimmo-Smith and Ince, 1969) was used for sample analysis. The report does not state if the analytical results, given in Table 5, were corrected for recovery.

Table 5. Residues of imidocarb in sheep, which received two IM doses, at a 7-day interval, of 1.2 mg/kg BW imidocarb dipropionate.

Withdrawal Time (days)	Range of Imidocarb Residues, mg/kg (n=3)					
	Liver	Kidney	Muscle	Fat	Initial Injection Site	Second Injection Site
7	5.7 - 14.3	22.6 - 121.2	1.1 - 1.2	<0.1 - 0.1	0.7 - 2.3	6.0 - 7.5
14	3.8 - 9.3	26.1 - 94.7	0.4 - 0.7	<0.1	<0.1 - 0.9	1.2 - 1.6
28	0.9 - 3.1	5.6 - 9.6	<0.1 - 0.4	<0.1	<0.1	0.2 - 1.0

In an earlier non-GLP study (Aliu *et al*, 1977), five sheep were injected IM with an aqueous solution of imidocarb dipropionate at a dose of 4.5 mg free base/kg BW. Individual sheep were killed at 4 h, 6 h and 32 days after dosing and two sheep were killed at 24 h after dosing. Tissue samples were analyzed using a spectrophotometric method described in the publication, with an estimated limit of detection of 5 mg/kg. The tissue distribution was similar to that observed

in the above study, but values are not cited due to the small number of animals (1 or 2) for each timepoint. Milk samples were also analyzed in this study (estimated limit of detection of 1 mg/L), with residues ranging from 4.5 - 5.6 mg/L in the 4 - 24 h samples. Again, since the dose was above the recommended level and the sample numbers very small, few conclusions can be drawn from the study.

METHODS OF ANALYSIS FOR RESIDUES IN TISSUES AND MILK

Analytical methods used in the early residue depletion studies were based on colorimetric (Nimmo-Smith and Ince, 1969; Aliu *et al*, 1977) or fluorometric (Nimmo-Smith and Norton, 1973) detection. Analytical sensitivity of these methods was limited in comparison to chromatographic techniques commonly used today in residue analysis and validation was not adequate by current standards. In particular, method specificity was poorly defined. These methods would not be suitable for use in a residue control program.

The first chromatographic method described used GC with alkali flame detection of imidocarb residues in milk after acid hydrolysis, diazotization and iodination (Taylor, 1981). However, the reliability of results generated with this method was not considered satisfactory, with the subsequent development of a GC/MS method which, while improving analytical reliability, still required the rather cumbersome hydrolysis and derivatization procedures (Crawley, 1982a).

More recent GLP studies have used analytical methodology based on HPLC with UV-detection, with the initial validation being for bovine muscle tissue (Gaffney, 1992). Muscle samples were homogenized in TRIS buffer, after which *Subtilisin Carlsberg* was added to release bound residues. Following incubation, the samples were acidified to precipitate protein, centrifuged and the supernatant was removed and made basic. Following removal of co-extractives with organic solvent, the aqueous extract was analyzed by HPLC under isocratic conditions on a cyano-bonded reverse phase column, with detection at 245 nm. Under the conditions of analysis, imidocarb eluted in 9 to 11 minutes, with nearly baseline resolution from co-extractives. Data demonstrated that imidocarb residues were apparently stable in muscle tissues stored at –20°C for up to a year. Subsequently, the method was modified to use a C-18 analytical column and applied to the analysis of bovine liver and muscle (Coldham *et al*, 1994; Coldham *et al*, 1995). Similar methodology was subsequently reported (Ferguson, 1996), with recovery data provided on fortified samples of bovine liver, kidney, muscle, fat and milk. Data generated in this study suggest some reduction in recovery of spiked imidocarb residues may occur in liver stored at –18°C for 54 days. Analytical results for fortified samples were: at a fortification level of 0.3 mg/kg; day 0, 0.24 mg/kg; day 54, 0.22 mg/kg; at a fortification level of 2.0 mg/kg; day 0, 1.76 mg/kg; day 54, 1.45 mg/kg. Performance characteristics reported for this method are summarized in Table 6.

Table 6. Performance characteristics of the liquid chromatographic assay for imidocarb residues in beef tissues and milk

Performance Characteristics	Liver	Kidney	Muscle	Fat	Milk
LOD (mg/kg)[1]	0.02	0.02	0.02	0.02	0.01
LOQ (mg/kg)	0.10	0.10	0.05	0.05	0.01[3]
Recovery (%)[2]	83.5	92.6	84.1	95.9	87.2
Precision (%)[2]	4.6	5.1	9.2	7.8	14.7

[1] The lowest calibration point having a signal-to-noise ratio greater than 3.
[2] Means of duplicate samples at 5 concentrations.
[3] The lowest concentration at which acceptable recovery was obtained.

An alternative approach has also been reported (Tarbin and Shearer, 1992), in which imidocarb residues in bovine kidney are determined following extraction in acetone under basic conditions, partitioning with chloroform, saturated aqueous salt and 40% sodium hydroxide, then clean up on a weak cation-exchange (carboxylic acid) solid phase extraction cartridge. The HPLC analysis on a C-18 column requires mobile phase switching and a column with a packing which is stable under various conditions of mobile phase pH. Total HPLC run time, including re-equilibration of the column, is 30 minutes. Detection is at 260 nm, with recoveries in the 75% range at 0.05 to 0.10 mg/kg and a claimed limit of detection of 0.001 mg/kg.

The HPLC methods described above appear suitable for regulatory use, although additional validation for appropriate species/matrix combinations is required. In addition, substitution of highly chlorinated solvents, such as chloroform, may be required.

APPRAISAL

Imidocarb had not been previously evaluated by the Committee.

Imidocarb is an anti-protozoal drug which has been used since the 1970's for the treatment of the protozoal diseases babesiosis in cattle and sheep and anaplasmosis in cattle. The preferred route of administration is by subcutaneous injection, but intramuscular injection may also be used.

Pharmacokinetic data

Rats Non-GLP pharmacokinetic studies using ^{14}C-imidocarb dipropionate and ^{14}C-imidocarb dihydrochloride were conducted in rats. In rats which received either of the imidocarb salts orally, absorption was poor, while subcutaneous injection with the dihydrochloride resulted in high residues at the injection site 7 days following treatment, with trace residues detectable in liver, kidney and muscle. In a non-GLP study, rats were dosed with unlabeled imidocarb at 10 mg/kg BW. Only about 19% of the dose, as parent compound, was excreted within 78 hours, with three-quarters of this in the urine. Multiple doses administered to rats by the oral or intraperitoneal route yielded highest tissue residues in kidney, followed by liver. A single SC injection of 5 mg/kg BW in rats revealed an initial half-life of residues in kidney and liver of about 3 days, increasing subsequently to 7-8 days. There was indication of significant tissue binding in liver. Administration of imidocarb dipropionate at 5 mg/kg BW by stomach tube, either using a single treatment or once daily for 30 days, resulted in residues in kidneys of about 10 mg/kg, while residues in liver were in the range of 1-2 mg/kg and in muscle were 0.5 mg/kg.

Mice Several non-GLP studies were also reported in mice. When mice were administered ^{14}C-imidocarb dihydrochloride by IV, excretion was rapid, with residues appearing in urine within 5 minutes of dosing and 90% of the drug was eliminated within 96 h (55-65% in urine and 23-25% in faeces). In mice sacrificed 3.5 h following IV administration of ^{14}C-imidocarb dihydrochloride, 29% of the dose was found in liver and 6.8% in kidney, with over 90% of the residue found in each tissue being parent compound. Parent compound also accounted for 95% of the residue found in urine.

Dog, monkey In a non-GLP study, dogs were administered 5 mg/kg BW imidocarb dipropionate once daily by gavage for 30 days and sacrificed at 24 hours after final treatment. Imidocarb was distributed as follows: liver, 98 mg/kg; kidney, 7.3 mg/kg; and muscle, <0.5 mg/kg. In a separate non-GLP study, the plasma half-life of imidocarb in dogs given an intravenous bolus dose of 4 mg/kg imidocarb dipropionate was 207 min, with approximately 80% of the dose eliminated within 8 h of treatment. In a non-GLP study using monkeys dosed orally once daily for 30 days with 5 mg/kg BW imidocarb dipropionate, imidocarb distribution in tissues was: liver, 1.02 mg/kg; kidney, 1.07 mg/kg; and muscle, <0.5 mg/kg.

Cattle Pharmacokinetic studies were conducted in cattle using ^{14}C-labeled and unlabeled imidocarb dipropionate. In a recent GLP study, cattle that were administered a single SC dose of 3 mg/kg BW of ^{14}C-imidocarb dipropionate had C_{max} of 1.32 mg/kg in blood within one hour of treatment. The concentration remained constant for 4 h, then declined to <0.05 mg/kg over the following 3 days. From 72-91% of the drug in blood was protein bound. Only 58% of the administered dose was eliminated over 28 days after treatment, distributed between faeces and urine in an approximately 3:1 ratio. Parent compound accounted for most of the residue in urine, but up to 28% of the residue found in faecal samples at 4 days post-dosing was an unidentified metabolite. The same metabolite accounted for 13% of the total residue in day 10 faecal samples, but was not present in samples tested at days 2 and 6. In tissues, the extractable portion without using enzymatic digestion of the total radioactive residue was: in liver, 81%; kidney, 94%; muscle, 89%; and milk, 81%. Parent imidocarb, as a fraction of total residue, was: liver, 68%; kidney, 88%; muscle, 88%; and milk, 77%. There was no apparent reduction in the proportion of parent compound to total residue observed for the various sampling dates. Other components present in extracts accounted for <10% of the total radioactive residue, indicating that metabolism is not significant. Tissue binding is most significant in liver, from which also the lowest proportion of the residue recovered is parent compound. This study confirmed findings of earlier non-GLP investigations where [^{14}C]imidocarb dipropionate was administered IM to cattle. A recent *in vitro* study using bovine liver gave no indication of any metabolism of imidocarb in this tissue.

In non-GLP studies in which calves received unlabeled imidocarb dipropionate intravenously or as a pour-on, distribution and elimination patterns were similar to those found in the recent GLP study reported above.

Sheep In several non-GLP studies conducted in sheep, IM administration of [^{14}C]imidocarb dipropionate resulted in distribution of residues throughout the central nervous system. Following IM injection at 4.5 mg/kg BW, C_{max} was 7.9 mg/L at about 4 hrs, after which concentrations declined slowly over 4 weeks to <0.1 mg/L, following first order kinetics. Significant protein binding was observed in plasma. There was no evidence of metabolite formation in urine, bile, liver and kidney samples. Urinary excretion was high within 24 h of treatment, declining rapidly afterwards.

Residue data

Cattle In dairy cattle and 9-month-old calves which received a single SC dose (3 mg/kg BW) of a formulation containing ^{14}C-imidocarb dipropionate, total residues in tissues (determined by combustion), collected at indicated withdrawal times, are reported in Table 7. These results demonstrate that elimination of residues is slow in all edible tissues. Total residues in milk reached a maximum 24 hrs following treatment (0.37 mg/L), declining to 0.10 mg/L at day 3 and to 0.02 mg/kg at day 8 and subsequent milking times through day 14.

Table 7. Total residues from a single SC dose of 3 mg/kg BW ^{14}C-imidocarb dipropionate to cattle.

	[^{14}C] -Imidocarb residues in tissues (mg/kg)				
Days Post-treatment	**Liver**	**Kidney**	**Muscle**	**Fat**	**Injection Site**
28 (6 cows)	8.24	12.81	0.68	0.13	1.73
56 (4 calves)	4.01	3.77	0.41	0.10	1.35
90 (4 calves)	2.19	1.40	0.31	0.03	0.54

In cattle treated with unlabeled imidocarb dipropionate (SC injection at 3 mg/kg BW), residues of parent compound in muscle tissue declined from 0.38 mg/kg at day 28 to 0.37 mg/kg at day 56 and to 0.21 mg/kg at day 98. Residues were still detectable in muscle (0.06 mg/kg) in animals slaughtered 224 days following treatment. Residues of parent compound in liver declined from 5.4 mg/kg at day 14 to 0.12 mg/kg at day 224. These tissue residue data are consistent with findings in earlier studies in which unlabeled imidocarb dipropionate was administered by IM or SC injection at various rates and in single or multiple doses. In two early non-GLP studies dairy cattle were treated by IM injection with imidocarb dipropionate at 3 mg/kg BW. Residues of parent compound in milk peaked at one day following treatment (0.60-0.79 mg/L), declined to 0.07-0.23 mg/L at day 3 and were <0.01 mg/L at days 7-28 following treatment. Milk samples, collected following administration of a second 3 mg/kg BW dose, gave similar depletion results after the day 28.

Sheep Several non-GLP studies were reviewed, including one in which 12 sheep received two IM injections at a rate of 1.2 mg/kg BW imidocarb dipropionate, with a 7-day interval between injections. At 7 days following the second treatment, residues in kidney ranged from 22.6 to 121.2 mg/kg, declining to 5.6-9.6 mg/kg at day 28. Residues in liver were from 5.7 to 14.3 mg/kg at day 7 and from 0.9 to 3.1 mg/kg at day 28, while in muscle, 1.1-1.2 mg/kg imidocarb was present at day 7, but <0.1 to 0.4 mg/kg remained at day 28. Residues in injection site muscle were higher than in normal muscle, but below residues in kidney and liver, for all sampling dates.

In 3 lactating sheep which received imidocarb dipropionate IM at 4.5 mg/kg BW, residues in milk ranged from 4.5 to 5.6 mg/L in samples collected from 4 to 24 h following treatment. The small numbers of animals involved and the methods and rates of dosing used limits the value of these studies in assessing residues.

Analytical methods

Recent GLP studies have used analytical methodology based on HPLC with UV-detection at 245 nm following treatment of tissues with enzymatic digestion to release residues, extraction, solvent partitioning, then clean-up by solid phase extraction. The performance characteristics of the method as reported by the sponsor are given in Table 8.

Table 8. Performance characteristics of the liquid chromatographic assay for imidocarb residues in beef tissues and milk

Performance Characteristic	Liver	Kidney	Muscle	Fat	Milk
LOD (mg/kg)[1]	0.02	0.02	0.02	0.02	0.01
LOQ (mg/kg)	0.10	0.10	0.05	0.05	0.01[3]
Recovery (%)[2]	83.5	92.6	84.1	95.9	87.2
Precision (%)[2]	4.6	5.1	9.2	7.8	14.7

[1] The lowest calibration point having a signal-to-noise ratio greater than 3.
[2] Means of duplicate samples at 5 concentrations.
[3] The lowest concentration at which acceptable recovery was obtained.

An alternative approach for the analysis of bovine kidney has also been reported using a weak cation-exchange solid phase extraction cartridge, followed by HPLC analysis on a C-18 column with UV-detection at 260 nm. This method requires mobile phase switching and a packed column that is stable under various conditions of the pH of the mobile phase, but should be within the capabilities of a typical residue laboratory. This method has the disadvantage that it includes a partitioning step with chloroform, which has been categorized as an ozone-depleting solvent. Recoveries are approximately 75% at 0.05 to 0.10 mg/kg and the limit of detection is 0.001 mg/kg.

The HPLC methods described above appear suitable for regulatory use, although additional validation for appropriate species/matrix combinations is required. In addition, alternatives for highly chlorinated solvents, such as chloroform, may be required.

Choice of marker residue

Imidocarb is the choice as marker residue in all tissues, although the radiolabel study in cattle did reveal the presence in some samples of small amounts of metabolites that constituted <10% of the total radioactivity. This study was used to establish the ratio of total residue to marker residue. The proposed regulatory method includes an enzyme digestion step, not included in the parent compound analysis in the radiolabel depletion study, but results should be comparable when corrected for recovery.

Maximum Residue Limits

In recommending MRL's, the Committee took into account the following factors:

- An ADI of 0-10 μg per kg of body weight was established, which results in a maximum ADI of 600 μg for a 60-kg person.
- The ratios of parent compound to total residues determined in the radiolabel study were as follows: liver, 68%; kidney, 88%; muscle, 88%; and milk, 77%. Data were not available for fat, so a factor based on the lowest ratio in liver was applied.
- Imidocarb is the appropriate marker residue. Liver and muscle are the recommended target tissues.
- A suitable analytical method is available for analysis of imidocarb residues in edible tissues and milk.

On the basis of the above considerations, the Committee recommended the following temporary MRL's for edible tissues of cattle and cattle milk, expressed as parent drug:

Tissue	Recommended MRL (μg/kg)	Food Factor (g)	MR/TR	Consumption (μg)
Muscle	300	300	0.88	102
Liver	2000	100	0.68	294
Kidney	1500	50	0.88	85
Fat	50	50	0.68	4
Milk	50 (μg/L)	1500	0.77	97

The MRL's recommended above would result in a theoretical daily maximum intake of 582 μg, based on a daily food intake of 300 g of muscle, 100 g of liver, 50 g each of kidney and fat and 1.5 L of milk.

The Committee requests that depletion studies be provided by 2001 in lactating and non-lactating cattle using the recommended SC dose of unlabeled imidocarb, and sample analysis using the proposed regulatory method with enzymatic digestion, before the temporary MRL's are considered for fully recommended MRL's. A depletion study is required in sheep, using the recommended dose and route of administration before MRL's can be considered for imidocarb as it is currently formulated.

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