

White Paper

Analytical validation of a point-of-care analyzer for electrolytes, pH, and hematocrit in dogs and cats

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Electrolyte analysis in companion animals is a standard diagnostic practice, useful both for sick or injured animals, and for healthy animals during annual health check-ups or pre-anesthetic evaluations. Electrolyte Point-Of-Care-Testing (POCT) is part of the routine in the veterinary practice and is mainly carried out using Blood Gas Analyzers (BGAs), validated for the veterinary use, which have a broad test menu but often require maintenance and are affected by downtime due to flushing and priming cycles. This study sought to validate the EXIAS e|1 Analyzer®, a POCT analyzer dedicated to electrolytes based upon ion-selective electrodes (ISEs) technology, currently used in human medicine, in dogs and cats. The analyzer is capable of measuring sodium (Na^+), potassium (K^+), chloride (Cl^-), ionized calcium (iCa^{2+}), pH, and hematocrit (Hct) and its introduction would reduce both maintenance and downtime compared to BGAs. Results demonstrate that the precision of the analyzer met the selected Westgard criterion ($\text{CV} < 5\%$) and was generally consistent with established literature data. For sodium, potassium, chloride and ionized calcium, the total observed error (TEobs) remained below the analyte-specific total allowable error (TEa) specifications. For hematocrit, TEobs (11.55%) met the selected expert-derived specification of 12.8%. Hematocrit results were systematically higher with the e|1 Analyzer than with the comparator analyzer, a difference that cannot be attributed to either instrument alone. For pH, the total observed error (0.050 pH units) slightly exceeded the specification of ± 0.04 pH units, although the mean systematic bias was very small (-0.0035 pH units). The analytical validation also compared the performance of the e|1 Analyzer to a BGA validated for companion animals. Method-comparison analysis, including Pearson correlation coefficients and Bland-Altman plots, demonstrated generally good agreement between the e|1 Analyzer and the veterinary comparator analyzer. Together with the analytical performance results, these findings supported evaluation of the transferability of the comparator analyzer reference intervals to the e|1 Analyzer. Verification of the transferred reference intervals in 20 apparently healthy dogs and 20 apparently healthy cats showed that all evaluated analyte/matrix combinations met the study-specific acceptance criterion of at least 18 of 20 compliant results. This comparator-based approach supports the transfer of the reference intervals to the e|1 Analyzer but does not establish e|1-specific reference intervals.

Introduction

In-house blood testing has become an integral part of companion-animal practice, offering immediate diagnostic results that support treatment decisions and routine or pre-anesthetic evaluations. Before an analyzer can be introduced into clinical practice, its analytical performance should be adequately characterized, particularly with regard to precision and accuracy. Appropriate reference intervals must also be available for the species in which the analyzer is intended to be used.

Electrolyte Point-Of-Care-Testing (POCT) is a standard part of the routine in veterinary practice. This testing is primarily conducted using Blood Gas Analyzers (BGAs), which are validated for veterinary use and possess a broad test menu.

However, the routine use of BGAs can be constrained by certain operational limits, depending on the analyzer. Some of these systems require maintenance, calibration, and flushing/priming cycles that may reduce operational readiness.

Depending on the platform, specimen types accepted may also be limited to whole blood, and the sample volume required can be difficult to obtain from small or debilitated patients.

Considering these operational constraints and maintenance demands, this study was initiated to validate an alternative POCT analyzer dedicated solely to

electrolytes (EXIAS e|1 Analyzer®, EXIAS Medical GmbH, Austria), which has reduced downtime, broad specimen acceptance and reduced sample volume, to assess its analytical performance in the veterinary practice. Similarly to BGAs, this system uses ion-selective electrodes (ISEs) technology and has been available for humans for over 6 years where, in addition to limited downtime and maintenance, it showed reliability comparable to the hospital reference methods [1].

It was important to verify that this analyzer, developed for human samples, could provide reliable results in companion animals, specifically dogs and cats.

The objective of the present study was to assess the analytical performance of the e|1 Analyzer in dogs and cats by evaluating precision and accuracy, comparing results with those obtained using a veterinary blood gas analyzer, and assessing the transferability and verification of reference intervals for the measured analytes (Na^+ , K^+ , Cl^- , iCa^{2+} , pH, Hct). The comparator device used for this purpose was the blood gas analyzer available in our practice [2, 3].

Figure 1 summarizes the analytical characteristics considered [4]. In addition, the comparison with a standard method was carried out to prove that reference intervals could be transferred to the e|1 Analyzer for the species considered [5, 6].

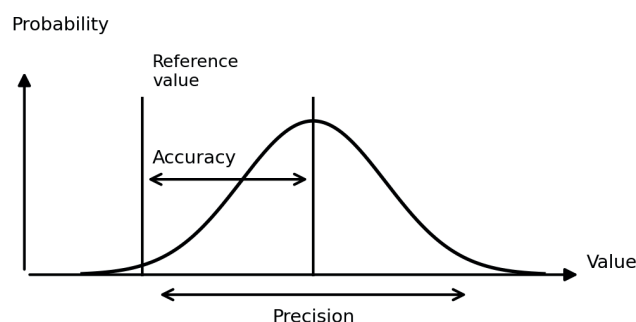


Figure 1: Schematic representation of analytical precision and accuracy, adapted from reference [4].

Materials and Methods

Equipment and Sample Handling

The EXIAS e|1 Electrolyte Analyzer was evaluated over a four-month period, from August to November 2023, at the Clinique Vétérinaire du Gour de l'Arche (CVGA, 247 route d'Angoulême 24000 Périgueux – France). It is a compact device (POCT) that uses cartridges containing all the components necessary for analyses (ion-selective electrodes (ISEs), reagents, control solutions, and sampling probes). Each of the cartridges used in the study enables conducting up to 600 samples and is valid for 42 days. A sample volume of only 20 μL is required for each test. Results are obtained in only 25 seconds. The results are printed immediately by the device and can be transmitted to an external software. Regular calibrations and integrated quality controls are carried out throughout the day. The measuring range of the e|1 Analyzer is presented in Table 1.

The comparator analyzer used was the Stat Profile® Prime VET from Nova Biomedical® (SPPV). The SPPV is also a compact device (POCT) that uses ISE cartridges, reagents, and control solutions that are independent of the ISE, along with a separate sampling probe. The cartridges are valid for 15 days, and the reagents last 1 month, allowing conducting 100 tests. A sample volume of 150 μL is required for each test. Results are obtained in 90 seconds. The results are printed immediately by the device and can be transmitted to an external software. Regular calibrations are carried out throughout the day. The measuring range of the SPPV is presented in Table 1. The SPPV has been in use at the facility since 2018. The SPPV has already been validated for veterinary practice [2, 3] and the manufacturer has defined a reference interval on this machine for the parameters studied in dogs and cats (data provided by Nova Biomedical®).

Parameters (units)	Measuring range	
	EXIAS e 1 Analyzer®	Stat Profile® Prime VET from Nova Biomedical®
Na ⁺ (mmol/L)	85 – 200	80 – 200
K ⁺ (mmol/L)	1.0 – 15.0	1.0 – 20.0
Cl ⁻ (mmol/L)	60 – 150	50 – 200
iCa ²⁺ (mmol/L)	0.10 – 3.20	0.20 – 2.70
pH	6.500 – 8.000	6.500 – 8.000
Hct %	10 – 75	12 – 70

Table 1: Measurement range of the EXIAS e|1 Analyzer® and the Stat Profile® Prime VET from Nova Biomedical® for Na⁺, K⁺, Cl⁻, iCa²⁺, pH, and Hct.

All e|1 Analyzer tests were performed on heparinized whole blood (HWB) with lithium heparinate immediately after sampling, followed by centrifugation at $12,000 \times g$ for 3 minutes and immediate testing of the resulting heparinized plasma (HP) on the e|1 Analyzer. The same HWB sample was tested on the SPPV before centrifugation. The lithium heparinate tubes used (25 IU/mL of blood) were Multivette 600® 0.6 mL tubes or Sarstedt® 1.3 mL lithium-heparin microtubes with orange push cap (ref. 41.1503.005).

Precision

To define the precision of the e|1 Analyzer for each parameter (Na⁺, K⁺, Cl⁻, iCa²⁺, pH, Hct), the within-run coefficients of variation (intra-run CV%) or repeatability were measured [7, 8]. The formula is $\text{CV}\% = (\text{SD}/\text{Mean}) \times 100$, where SD is the standard deviation and Mean is the average. These measurements were performed on quality control solutions with three different control levels (QC1, QC2, QC3) and on heparinized blood from a healthy dog, with 10 successive measurements on the same sample each time, designated as intra-run CV(QC1 or QC2 or QC3) and intra-run CV(ND), respectively. The intra-run CV(ND) were defined for both HWB and HP for each parameter, except for Hct (only heparinized whole blood was used). The values of the different parameters for each control solution are explained in detail in Table 2.

	QC 1	QC 2	QC 3
Na ⁺ (mmol/L)	116.2-124.4	132.8-141.0	155.5-165.1
K ⁺ (mmol/L)	1.49-2.31	4.07-4.89	6.14-6.96
Cl ⁻ (mmol/L)	76.2-88.2	93.9-105.9	124.4-137.4
iCa ²⁺ (mmol/L)	1.312-1.632	0.924-1.244	0.396-0.716
pH	7.066-7.184	7.344-7.462	7.584-7.704
Hct %	54.5-62.5	38.8-46.8	17.2-25.2

Table 2: EXIAS® manufacturer-assigned ranges for quality-control materials QC1, QC2 and QC3.

The inter-run coefficients of variation or between-run imprecision (inter-run CV%) were also measured for each parameter, on QC1, QC2, QC3 at the same time, and on the HP from a dog, with 10 measurements taken on the same sample at one-day intervals over 10 consecutive days, designated as inter-run CV (QC1 or QC2 or QC3) and inter-run CV(ND) respectively [7, 8]. A new control solution identical to the previous one was used each day. The HP from the healthy dog was divided into 10 aliquots and stored at 4°C for 10 days [5]. Because this plasma was stored for 10 days, the observed between-run variability may include pre-analytical effects in addition to analyzer imprecision, particularly for pH and $i\text{Ca}^{2+}$.

Total Observed Error (TEobs)

To assess the analytical performance of the e|l Analyzer relative to predefined quality specifications, tests were performed on the HWB from a healthy dog to compare the values obtained with the comparator analyzer (SPPV) to those obtained with the e|l Analyzer for each parameter (Na^+ , K^+ , Cl^- , $i\text{Ca}^{2+}$, pH, Hct). All tests were conducted immediately after sampling. Observed total error (TEobs) was estimated as the absolute mean signed bias plus twice the standard deviation (SD), or equivalently as the absolute relative bias plus twice the coefficient of variation (CV) when expressed as a percentage. The mean signed bias was calculated as the mean difference between the e|l Analyzer and SPPV results (e|l minus SPPV), and the relative bias (%) as its absolute value divided by the mean SPPV value, multiplied by 100 [8]. For ionized calcium and pH, TEobs was additionally expressed in the original measurement units (mmol/L and pH units, respectively) to allow direct comparison with published absolute allowable-error specifications [9, 10]. TEobs was compared with the total allowable error (TEa) specified for each parameter. The source of each specification is given in Table 5.

Method Comparison

Samples were collected over 15 days (from 31/08/2023 to 13/09/2023) from dogs and cats presented for routine clinical care at the CVGA clinic, including apparently healthy and diseased animals, after obtaining consent from the owners. 63 dogs and 28 cats were tested during this period. The samples were systematically analyzed three times: on HWB using the SPPV and the e|l Analyzer, and on HP using the e|l Analyzer. Pearson r was calculated for each analyte to describe the linear association between e|l Analyzer and SPPV measurements [12]. The Pearson r coefficients of correlation define a very high degree of correlation if $r \geq 0.90$; a high degree of correlation if $0.70 \leq r \leq 0.89$; a moderate degree of correlation if $0.50 \leq r \leq 0.69$; a low degree of correlation if $0.30 \leq r \leq 0.49$; and a minimal or non-existent degree of correlation if $0.0 \leq r \leq 0.29$ [13]. Agreement between the two analyzers was further assessed using Bland-Altman analysis. For each paired measurement, the difference between the two methods was plotted against the mean

of the two measurements. Mean bias and 95% limits of agreement (mean difference $\pm$ 1.96 SD) were displayed for each analyte [14].

Verification of Transferred Reference Intervals

Blood samples were collected over two weeks (from 08/11/2023 to 21/11/2023) from 20 apparently healthy dogs and 20 apparently healthy cats, analyzed on the SPPV using HWB (to check if the values of each parameter were within or outside the reference interval (RI) of the SPPV) and on the e|l Analyzer using HWB and HP. Tests were performed immediately after sampling. The existing SPPV reference intervals were considered candidate intervals for transfer to the e|l Analyzer. Transferability was considered successfully verified when at least 18 of 20 results obtained with the e|l Analyzer met the predefined acceptance criterion [15, 16]. Otherwise, 20 more animals would be sampled, with the same methodology being applied [15]. When both the e|l Analyzer and SPPV results for a given analyte fell outside the candidate reference interval in the same direction, this was interpreted as compatible with individual biological variation rather than, by itself, evidence of failed reference-interval transfer. An e|l result outside the candidate interval with a concurrent in-range SPPV result was considered discordant.

Results

Table 3 presents the intra-run CV% of the e|l Analyzer. All values obtained for each parameter on QC1, QC2, and QC3 were within the manufacturer-assigned ranges for quality-control materials QC1, QC2 and QC3 (Table 2). All values obtained for each parameter, whether from QC1, QC2, QC3, or HWB or HP, complied with Westgard recommendations ($\text{CV} < 5\%$) [7]. For QC1, QC2, and QC3, all intra-run CV% are consistent with those described in the literature [2, 14, 17, 18, 19].

For Na^+ , K^+ , and Cl^- , the intra-run CV% on HWB and HP are consistent with those described in the literature [2, 14]. For $i\text{Ca}^{2+}$ and pH, the intra-run CV% on HWB conforms to those described in the literature, which is not the case for HP [2, 17, 18]. This deviation for $i\text{Ca}^{2+}$ and pH is most plausibly attributed to pre-analytical influences – particularly sensitivity to anaerobic handling and CO_2 exchange, rather than to analytical performance limitations; consequently, these results should not be interpreted as reflecting analytical imprecision alone. For Hct, obtaining intra-run CV% on HP is not possible (as plasma does not contain erythrocytes); the intra-run CV% on HWB conforms to those described in the literature [19].

Table 4 presents the inter-run CV% of the e|l Analyzer. All values obtained for each parameter on QC1, QC2, and QC3 were within the manufacturer-assigned ranges for quality-control materials QC1, QC2 and QC3 (Table 2). All values obtained for each parameter, whether from QC1, QC2, QC3, or on HP, complied with Westgard recommendations ($\text{CV} < 5\%$) [7]. For QC1, QC2, and QC3, all inter-run CV% are consistent with

those described in the literature [2, 17, 18, 20]. For $i\text{Ca}^{2+}$ and pH, the observed inter-run CV% on HP exceeds values reported in the literature [2, 17, 18]. This deviation is most plausibly attributed to pre-analytical influences – particularly sensitivity to anaerobic handling and CO_2 exchange – rather than to analytical performance limitations; as above, these results should not be interpreted as reflecting analytical imprecision alone. In contrast, Na^+ , K^+ , and Cl^- show inter-run imprecision fully compliant with published data [2, 14]. For Hct, obtaining inter-run CV% on HP is also not possible [20].

Table 5 presents the total observed error (TEobs) results of the e|1 Analyzer in comparison to the comparator analyzer (SPPV) for each parameter. For Na^+ , K^+

and Cl^- , the observed total errors (1.80%, 3.73% and 3.93%, respectively) were below the selected allowable-error specifications [8]. For ionized calcium, the absolute observed total error was 0.1098 mmol/L, below the WSLH allowable-error specification of ± 0.13 mmol/L [10]. For pH, the estimated total observed error was 0.0503 pH units, slightly exceeding the selected CLIA specification of ± 0.04 pH units [9]. However, the mean signed bias was only -0.0035 pH units, and nine of the ten individual measurements were within the specified tolerance. For hematocrit, the observed total error was 11.55%, below the selected expert-derived allowable-error specification of 12.8% at a hematocrit decision level of 0.39 L/L [11].

Parameters (units)	QC1 (CV%)	QC2 (CV%)	QC3 (CV%)	Healthy dog HWB and HP (CV%)	Reference [2, 14, 17, 18, 19]	Westgard Recommendations (CV%)
Na^+ (mmol/L)	0.33	0.34	0.31	0.25 (HWB) 0.34 (HP)	0.32-1.42	< 5%
K^+ (mmol/L)	1.14	0.32	0.28	0.56 (HWB) 1.36 (HP)	0.23-2.50	
Cl^- (mmol/L)	0.61	0.50	0.42	0.47 (HWB) 0.27 (HP)	0.50-1.80	
$i\text{Ca}^{2+}$ (mmol/L)	0.65	0.67	0.47	0.99 (HWB) 3.25 (HP)	0.39-2.32	
pH	0.05	0.02	0.02	0.31 (HWB) 0.72 (HP)	0.02-0.39	
Hct %	2.27	0.38	1.35	0.37 (HWB) Ø (HP)	3.10-3.20	

Table 3: Within-run imprecision (CV%) of the EXIAS e|1 Analyzer® using three quality-control levels (QC1, QC2, QC3) and samples from an apparently healthy dog, analyzed as heparinized whole blood (HWB) and, where applicable, heparinized plasma (HP).

Parameters (units)	QC1 (CV%)	QC2 (CV%)	QC3 (CV%)	Healthy dog HWB and HP (CV%)	Reference [2, 14, 17, 18, 19]	Westgard Recommendations (CV%)
Na^+ (mmol/L)	0.20	0.27	0.24	0.44	0.11-1.30	< 5%
K^+ (mmol/L)	0.49	0.46	0.28	0.75	0.17-2.50	
Cl^- (mmol/L)	0.26	0.52	0.28	1.08	0.42-1.80	
$i\text{Ca}^{2+}$ (mmol/L)	0.55	0.49	0.71	2.72	0.04-2.20	
pH	0.02	0.02	0.02	0.74	0.01-0.02	
Hct %	0.31	0.40	0.98	Ø	0.48-3.7	

Table 4: Between-run imprecision (CV%) of the EXIAS e|1 Analyzer® using control solutions QC1, QC2, and QC3 and heparinized plasma (HP) from a healthy dog

Parameters	Bias	Intra-run CV (%) / SD	TEobs	Total allowable error Units: % unless otherwise stated – see caption
Na ⁺ (mmol/L)	1.30%	0.25%	1.80%	< 5 [8]
K ⁺ (mmol/L)	2.61%	0.56%	3.73%	< 5 to 10 [8]
Cl ⁻ (mmol/L)	2.99%	0.47%	3.93%	< 5 [8]
iCa ²⁺ (mmol/L)	0.0842 mmol/L (7.02%)	SD 0.01279 mmol/L (CV 1.00%)	0.1098 mmol/L (9.02%)	± 0.13 mmol/L [10]
pH	0.0035 pH units (0.05%)	SD 0.02342 pH units (CV 0.32%)	0.0503 pH units (0.68%)	± 0.04 pH units [9]
Hct %	10.81%	0.37%	11.55%	< 12.8 [11]

Table 5: Total observed error (TEobs) of the EXIAS e|I Analyzer® for measurements performed on heparinized whole blood, using the Stat Profile® Prime VET as the comparator analyzer. Published total allowable error (TEa) specifications and their sources are shown for comparison. Values are given in % unless otherwise stated. For iCa²⁺ and pH, bias, SD and TEobs are given in the original units, with the corresponding percentages in parentheses, and are compared with absolute specifications (WSLH ±0.13 mmol/L for iCa²⁺ [10], CLIA ±0.04 pH units for pH [9]). For K⁺, a TEa of 10% applies to low concentrations and 5% to normal and high concentrations [8]. The Hct TEa of 12.8% is an expert-derived specification at a hematocrit decision level of 0.39 L/L [11]. TEobs was calculated from unrounded values.

	Na ⁺		K ⁺		Cl ⁻		iCa ²⁺		pH		Hct
	HWB	HP	HWB	HP	HWB	HP	HWB	HP	HWB	HP	HWB
r (Dog)	0.77	0.79	0.96	0.99	0.72	0.97	0.97	0.85	0.94	0.67	0.97
r (Cat)	0.89	0.99	0.97	0.99	0.64	0.78	0.95	0.97	0.96	0.94	0.99

Table 6: Pearson (r) coefficients of correlation for different parameters on heparinized whole blood (HWB) and heparinized plasma (HP), using the Stat Profile® Prime VET from Nova Biomedical® as the comparator analyzer, in up to 63 dogs (62 paired measurements for Na⁺, K⁺, Cl⁻, iCa²⁺, and pH; 61 for Hct) and 28 cats.

Parameters HWB and /or HP (units)	Proposed Dog RI (See SPPV RI)	Proposed Cat RI (See SPPV RI)	Verification with 20 animals: Yes (O) if ≥ 18/20 compliant with the proposed RI No (N) if < 18/20 compliant with the proposed RI
Na ⁺ (mmol/L) HWB & HP	138.0 – 151.0	143 – 156	O: D 20/20 (HWB & HP) C 20/20 (HWB) & 19/20 (HP)
K ⁺ (mmol/L) HWB & HP	3.60 – 5.80	3.6 – 5.8	O: D 20/20 (HWB & HP) C 20/20 (HWB & HP)
Cl ⁻ (mmol/L) HWB & HP	106.0 – 121.0	112 – 134	O: D 19/20 (HWB & HP) C 20/20 (HWB & HP)
iCa ²⁺ (mmol/L) HWB	1.160 – 1.400	1.100 – 1.330	O: D 18/20 C 18/20
pH HWB	7.340 – 7.460	7.250 – 7.410	O: D 19/20 C 18/20
Hct (%) HWB	36.0 – 55.0	24.0 – 45.0	O: D 20/20 C 20/20

Table 7: Reference intervals (RI) of the Stat Profile® Prime VET from Nova Biomedical® (SPPV) transferred to and verified on the EXIAS e|I Analyzer® for Na⁺, K⁺, Cl⁻, iCa²⁺, pH, and Hct on heparinized whole blood (HWB), and for Na⁺, K⁺, and Cl⁻ on heparinized plasma (HP), in dogs (D) and cats (C).

Table 6 shows the Pearson (r) coefficients of correlation calculated from the results obtained from the 63 dogs and 28 cats that were tested.

The degrees of correlation between the e|1 Analyzer and the SPPV are high to very high for all measured parameters, whether on HWB or HP, except for pH on HP in dogs and for Cl^- on HWB in cats, where the degrees of correlation are moderate [13]. As noted above, Pearson r describes the linear association between the two analyzers; agreement between methods was assessed separately using Bland-Altman analysis.

Figures 2 and 3 represent the correlations of results obtained from 63 dogs and 28 cats respectively (62 paired measurements for Na^+ , K^+ , Cl^- , iCa^{2+} , and pH, and 61 for Hct in dogs; 28 for all analytes in cats), with the e|1 Analyzer and SPPV for different parameters on HWB with the calculated r values, as well as the obtained Bland-Altman diagrams. Bland-Altman analysis

showed that most paired measurements fell within the calculated 95% limits of agreement. Systematic differences between analyzers were nevertheless observed for some analytes and are discussed below.

To verify the transferability of the SPPV reference intervals to the e|1 Analyzer, samples were taken from 20 dogs and 20 cats (apparently healthy), assessing whether at least 18 out of 20 dogs and 18 out of 20 cats had e|1 results for each parameter consistent with the SPPV reference interval, applying the study-specific comparator rule described above [16]. The results obtained (see Table 7) indicated successful verification of the transferred reference intervals for all parameters in dogs and cats (18/20 to 20/20 of results met the acceptance criterion, depending on the parameter) [15]. The reference intervals for Na^+ , K^+ , and Cl^- were verified on both HWB and HP. The reference intervals for iCa^{2+} , pH, and Hct were verified on HWB only.

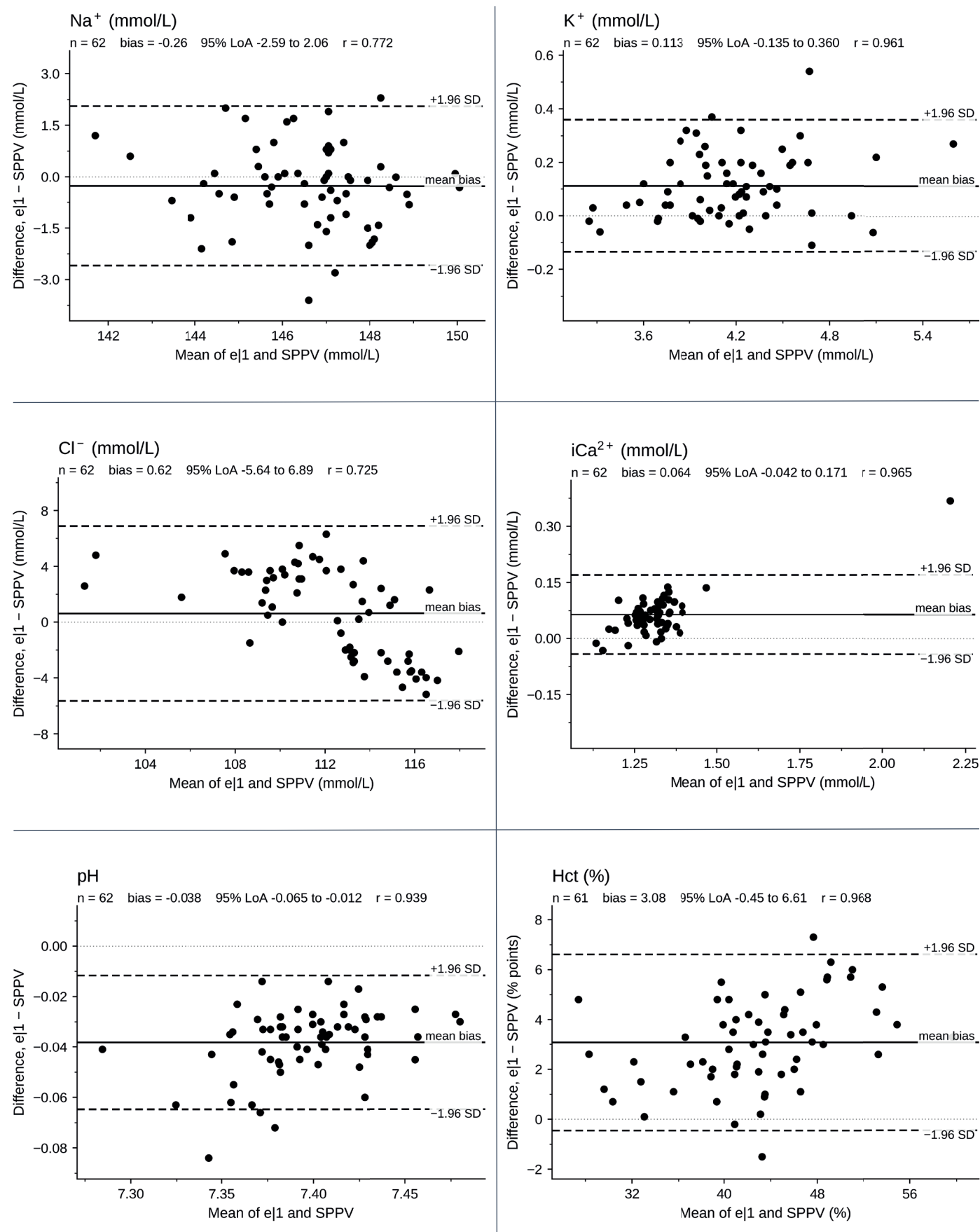


Figure 2: Bland-Altman analysis of the EXIAS e|1 Analyzer® against the Stat Profile® Prime VET in canine heparinized whole blood. For each analyte the difference between methods (e|1 – SPPV) is plotted against the mean of the two measurements. The continuous horizontal line indicates the mean bias and the dashed lines the 95% limits of agreement (mean bias ± 1.96 SD). The dotted line marks zero difference. The number of paired measurements (n), mean bias, 95% limits of agreement and the Pearson correlation coefficient (r) are given for each analyte.

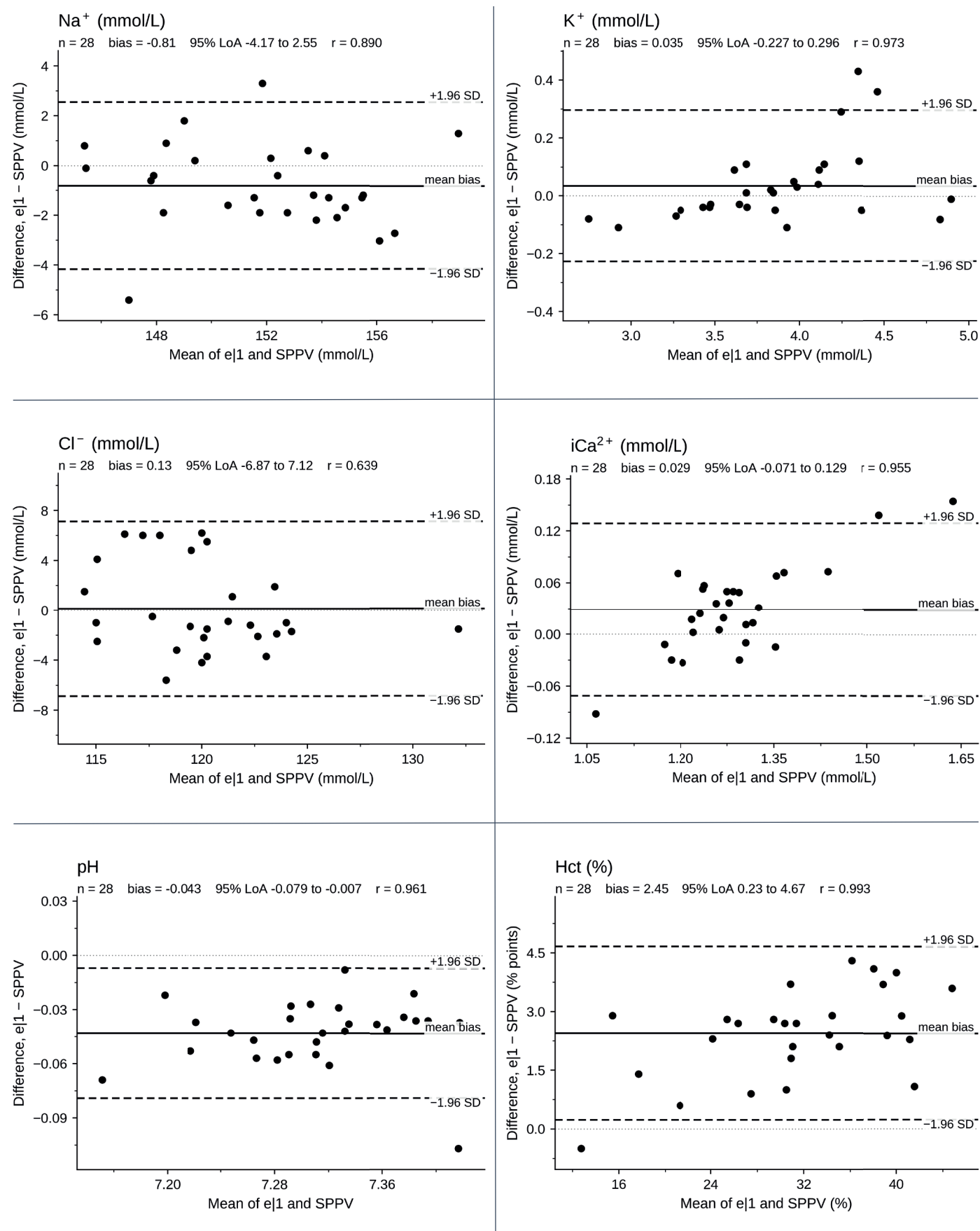


Figure 3: Bland-Altman analysis of the EXIAS e|1 Analyzer® against the Stat Profile® Prime VET in feline heparinized whole blood. Panel structure, axis conventions and annotations are identical to Figure 2. Twenty-eight paired measurements were available for each analyte.

Discussion

This study found that the e|l Analyzer demonstrated high precision and a total observed error (TEobs) within the selected specifications for Na^+ , K^+ , Cl^- , iCa^{2+} and Hct. For pH, the total observed error of 0.0503 pH units slightly exceeded the CLIA criterion of ± 0.04 pH units [9], despite a very small mean bias. Agreement with the comparator analyzer in the method-comparison analysis was analyte-dependent, with systematically higher hematocrit results on the e|l Analyzer.

The EXIAS e|l Electrolyte Analyzer (EXIAS Medical GmbH, Austria) measures six parameters in approximately 25 seconds from canine or feline blood samples: Na^+ , K^+ , Cl^- , iCa^{2+} , pH, and Hct. Sodium, potassium, and chloride can be measured in both heparinized whole blood (HWB) and heparinized plasma (HP). Heparinized whole blood is the preferred sample matrix for ionized calcium and pH measurements, whereas hematocrit can only be determined in whole blood. These blood parameters are useful in veterinary practice, both for sick or injured animals [21, 22, 23, 24, 25, 26, 27, 28] and for healthy animals during annual health check-ups or pre-anesthetic evaluations [29].

For iCa^{2+} , pH, and Hct, it is crucial to obtain results at the patient's bedside. In fact, the time required to send the samples to an external testing facility can lead to changes in these parameters due to sample aging and lack of stability [17, 30]. Exposure of the sample to ambient air may alter PCO_2 and pH and consequently affect measured iCa^{2+} ; the heparin content of the collection tube can also influence the result, with higher heparin concentrations associated with lower measured iCa^{2+} [30]. For pH, the analysis must also be performed anaerobically [30], while Hct tends to increase over time [31].

To evaluate the precision of the e|l Analyzer, in addition to using control solutions provided by the manufacturer, we used canine samples (HWB and HP) to closely mimic the pre-analytical and analytical conditions that are commonly encountered in veterinary practice. The results were excellent in both cases. The precision of the e|l Analyzer, whether in repeatability (intra-run CV%) or between-run imprecision (inter-run CV%), is excellent and consistent with the literature data regarding CV [2, 14, 17, 18, 19, 20], and validates Westgard recommendations [7] for all control solutions (QC1, QC2, and QC3), for all parameters on HWB, and for Na^+ , K^+ , and Cl^- on HP. These results confirm that measurements of iCa^{2+} and pH should be performed on HWB (and, evidently, Hct as well) [30].

The analytical performance of the EXIAS e|l Analyzer was generally favorable under the conditions evaluated. Sodium, potassium, chloride, and ionized calcium met the selected allowable total error specifications (Table 5). For ionized calcium, an absolute allowable-error criterion was considered more appropriate than a fixed percentage, since the corresponding relative allowable error depends on the calcium concentration. For hematocrit, the TEa of 12.8% is an expert-derived spe-

cification corresponding to a hematocrit decision level of 0.39 L/L [11], and the observed Hct TEobs of 11.55% meets this selected specification. The same expert-derived TEa specification of 12.8% for hematocrit was also used to evaluate the analytical performance of veterinary point-of-care hematology analyzers [32]. This TEa is concentration-dependent, and stricter quality specifications have also been published, for example $\pm 6\%$ under CLIA [9].

The method-comparison data also showed systematically higher hematocrit results with the e|l Analyzer than with the Stat Profile Prime VET in both dogs and cats. Since the comparator was another point-of-care analyzer rather than a centrifuged packed cell volume reference method, this difference cannot be attributed exclusively to either instrument.

Because analytical performance specifications for pH are commonly expressed in absolute pH units rather than percentages, the pH TEobs was also expressed in pH units. At 0.0503 pH units, the estimated total observed error slightly exceeded the CLIA specification of ± 0.04 pH units [9]. Nevertheless, the mean signed bias was very small, and nine of the ten individual measurements were within the specified tolerance. These findings suggest limited systematic disagreement at the concentration evaluated, although the observed variability prevented the estimated total error from meeting the selected quality goal. Importantly, these total-error estimates were derived from repeated measurements of a single canine whole-blood sample and should not be generalized to the entire measurement ranges or to feline samples. Together with the method-comparison results, these findings supported further evaluation of the transferability of the SPPV reference intervals to the e|l Analyzer [8].

Pearson correlations were high to very high for most parameter combinations; as noted above, r describes association rather than agreement. Differences between HWB and HP for pH and iCa^{2+} may reflect pre-analytical handling but cannot be separated from analytical effects in this study [30, 33, 34].

Given the precision, TEobs, and method-comparison results of the e|l Analyzer relative to the SPPV, we proceeded to assess the transferability of the SPPV reference intervals to the e|l Analyzer for each of the six parameters: Na^+ , K^+ , Cl^- , iCa^{2+} , pH, and Hct. De novo establishment of reference intervals generally requires a substantially larger reference population, with at least 120 reference individuals commonly recommended for non-parametric determination. When an established reference interval is transferred to another analytical system, a smaller verification study may be used [15, 16]. In this study, an existing reference interval was considered successfully verified if 18 or more of 20 results obtained with the e|l Analyzer met the predefined acceptance criterion [15]. This represents a study-specific adaptation of the conventional 20-individual verification approach and should therefore be interpreted as supportive evidence

for reference-interval transfer rather than as de novo establishment of e|l-specific reference intervals.

This study-specific approach involved simultaneously verifying with the comparator analyzer (SPPV) that the tested animal, which appears to be healthy, has a value for each tested parameter within the candidate RI. Testing six parameters on each individual increases the probability of finding at least one parameter outside the reference interval by chance alone; assuming independence among analytes, this probability rises from 5% for a single parameter to approximately 26% for six parameters ($1 - 0.95^6$). This calculation assumes independence among analytes, which may not hold in practice, and should be interpreted as an illustrative approximation only. In some cats, sedation or anesthesia was required, which represents a potential source of biological variation and a limitation of this study rather than a proven cause of the individual out-of-range results observed [35, 36, 37]. Electrolyte anomalies are frequently reported in the context of pre-anesthetic evaluations [29], and stress in cats may also contribute to such variation [30].

For these reasons, results falling outside the candidate reference interval on both analyzers, in the same direction, were considered concordant for the purposes of this study-specific verification procedure. An e|l result outside the candidate interval while the concurrent SPPV result remained within range was considered discordant. The simultaneous use of the comparator analyzer provided additional information for interpreting out-of-range results during reference-interval verification.

For Na^+ , K^+ , and Cl^- , both HWB and HP were suitable under the conditions evaluated. For pH and iCa^{2+} , HWB was retained as the preferred matrix because it showed lower imprecision and requires less pre-analytical manipulation. Hct can only be measured in whole blood. Results for iCa^{2+} apply to the lithium-heparin tubes used (25 IU/mL of blood; Multivette 600® 0.6 mL or Sarstedt® 1.3 mL microtubes, ref. 41.1503.005): excess heparin can decrease measured iCa^{2+} , so appropriate tube filling is important [30].

During the study, the instrument provided results within approximately 25 seconds and required no routine operator maintenance other than cartridge replacement according to the manufacturer's operating procedure.

Limits of this study reside in being the very first assessment of the e|l Analyzer. Validation on a larger scale is needed to confirm the analytical performance of the analyzer and to refine the RIs within larger populations of dogs and cats. Moreover, introducing the use of the e|l Analyzer to additional species would require additional studies to assess RIs for each of the species considered. Additional limitations include the single-center, single-analyzer design of the present study, as well as the limited size of the reference-interval verification cohorts. Other contributing factors were out-of-range comparator results in some apparently healthy animals, possible sedation- or stress-related effects in cats, stored-plasma pre-analytical effects on between-run variability, and the study-specific nature of the reference-interval verifica-

tion approach.

A further limitation concerns the reference-interval verification procedure. A few individual feline results were markedly outside the proposed reference intervals on both instruments. Some cats included in the verification cohort were undergoing routine pre-anesthetic laboratory screening, and these markedly abnormal results were discovered incidentally, despite the absence of clinically apparent abnormalities at the time of sampling. Under the predefined study-specific comparator rule, results outside the candidate interval in the same direction on both analyzers were considered concordant. Nevertheless, such concordance does not establish that the animals were biologically healthy or that the measurements were analytically accurate.

Conclusion

Under the conditions evaluated, the EXIAS e|l Electrolyte Analyzer demonstrated high analytical precision and generally favorable performance for the measurement of electrolytes, pH, and hematocrit in dogs and cats. The selected allowable total error specifications were met for sodium, potassium, chloride, ionized calcium, and hematocrit in the single-sample analytical assessment. For pH, the estimated total error slightly exceeded the selected CLIA criterion, despite a very small mean systematic bias. Hematocrit results were systematically higher than with the comparator analyzer, a difference that cannot be attributed to either instrument alone.

Method comparison with the Stat Profile Prime VET showed analyte-dependent agreement, and the transferred reference intervals met the study-specific verification criterion of at least 18 of 20 compliant results in the populations examined. This comparator-based approach does not establish e|l-specific reference intervals, and concordant out-of-range results do not prove biological normality. Heparinized whole blood is preferred for pH, iCa^{2+} , and Hct, while both heparinized whole blood and heparinized plasma are suitable for sodium, potassium, and chloride. Further multicenter studies would be valuable to confirm analytical performance across wider concentration ranges and in larger canine and feline populations.

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Declarations

Ethics approval and consent to participate:

Samples and clinical data used in this study were obtained from dogs and cats presented to the Clinique Vétérinaire du Gour de l'Arche as part of routine veterinary care. No additional sampling or procedures were performed solely for the purposes of this study, and no additional discomfort was caused to the animals. Informed consent for the use of samples and data was obtained from the owners.

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Ludovic Simeon conducted the study, analyzed the data, and prepared the manuscript, tables, and figures.

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Conflicts of Interest:

The author reports having acted as a consultant for EXIAS Medical GmbH and Nova Biomedical. EXIAS Medical GmbH provided the e|l Analyzer and consumables used in this study.