

# Establishment of Historical Control Reference Values of Cambodian Cynomolgus Macaque Blood Gases

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## Abstract

Measuring blood gases can be useful in helping to identify drug-related respiratory changes like blood changes in the diffusion of gases from the lungs into the bloodstream. For small molecule pharmaceuticals, ICH S7 identifies hemoglobin oxygen saturation (sO<sub>2</sub>) as a potential part of the core respiratory battery, while other blood gases (e.g. pO<sub>2</sub> and pCO<sub>2</sub>) can be used for supplemental assessment. However, there is a paucity of data describing the normal blood gas ranges in cynomolgus macaques. To assist and improve the assessment of drug-related changes to cynomolgus macaque blood gasses, arterial blood gas was collected from 98 male and 94 female cynomolgus macaques. All animals were test-article naïve, with all collections performed while they were conscious and restrained. The analysis determined that no differences existed between males and females in most parameters investigated. For example, sO<sub>2</sub> and pO<sub>2</sub> values were 97.7% and 94.9 mmHg in both sexes, while pCO<sub>2</sub> values were 30.9 and 32.2 mmHg in males and females, respectively.

## Introduction

Tidal volume or hemoglobin oxygen saturation should be evaluated in order to assess ICH S7 respiratory function as part of the safety pharmacology core battery. However, no robust research data has been published about normal ranges for blood gases for cynomolgus macaque in a preclinical laboratory setting. This can lead to some difficulties in interpreting and identifying an effect on these parameters. Using data from approximately 100 male and 100 female cynomolgus macaques, different blood gas parameters were evaluated to better define a normal range for interpretation in nonclinical studies.

## Material and Methods

### Animals and Animal Care

**Test System:** *Macaca fascicularis*, male and female, 2 to 10 years old, 1.6 to 10 kg

**Source:** Cambodia

**Approval for Research:** All animal-related procedures were approved by the IACUC.

**Environmental Conditions:** Primary enclosure complied with the Animal Welfare Act and recommendations set forth in the Guide for the Care and Use of Laboratory Animals (National Research Council 2011). Animals were housed in a temperature- and humidity-controlled environment with target ranges between 18 and 29 degrees Celsius, and 30 and 70%, respectively. A 12-hour light/dark cycle was set, and animals were kept in stainless steel metal cages.

**Diet:** PMI LabDiet® Fiber-Plus® Monkey Diet 5049 biscuits, and water were provided ad libitum. Treats were provided daily and included fresh produce, marshmallows, raisins, juice, etc.

### Arterial Blood collection

Arterial blood was collected into heparinized syringes once from awake, restrained animals. All collections were performed prior to animals receiving any test article.

### Blood Gas Analysis

Arterial blood was analyzed fresh with Abbot i-STAT 1® point-of-care analyzer via CG4+ or CG8+ cartridges to determine the following parameters: oxygen saturation (sO<sub>2</sub>), partial pressure in oxygen (pO<sub>2</sub>), partial pressure in carbon dioxide (pCO<sub>2</sub>), pH, base excess concentration, bicarbonate concentration, and total carbon dioxide concentration.

### Data Evaluation

Average, standard deviation, and percentiles (5% and 95%) were determined. A t-test was performed for all parameters to evaluate a potential difference between the data obtained from male and female animals.

The data distribution was also evaluated by determining the incidence per 10 ranges, as defined by the data set.

## Results

**Table 1. Blood gas parameters obtained from 98 male cynomolgus macaques**

	Average	SD	Min	Max	Percentile 5%	Percentile 95%
S02 (%)	97.7	0.91	95.0	99.0	96.0	99.0
P02 (mmHg)	95.0	11.49	68.0	142.0	77.9	112
PCO2 (mmHg)	32.2	3.23	20.3	40.4	27.4	37.2
pH	7.46	0.070	7.17	7.58	7.33	7.55
Base Excess (millimoles/liter)	-0.398	5.7174	-21.0	8.0	-11.0	7.0
HCO3 (millimoles/liter)	23.4	4.69	7.50	30.90	15.5	30.0
TCO2 (millimoles/liter)	24.4	4.74	8.00	32.00	16.9	31.0

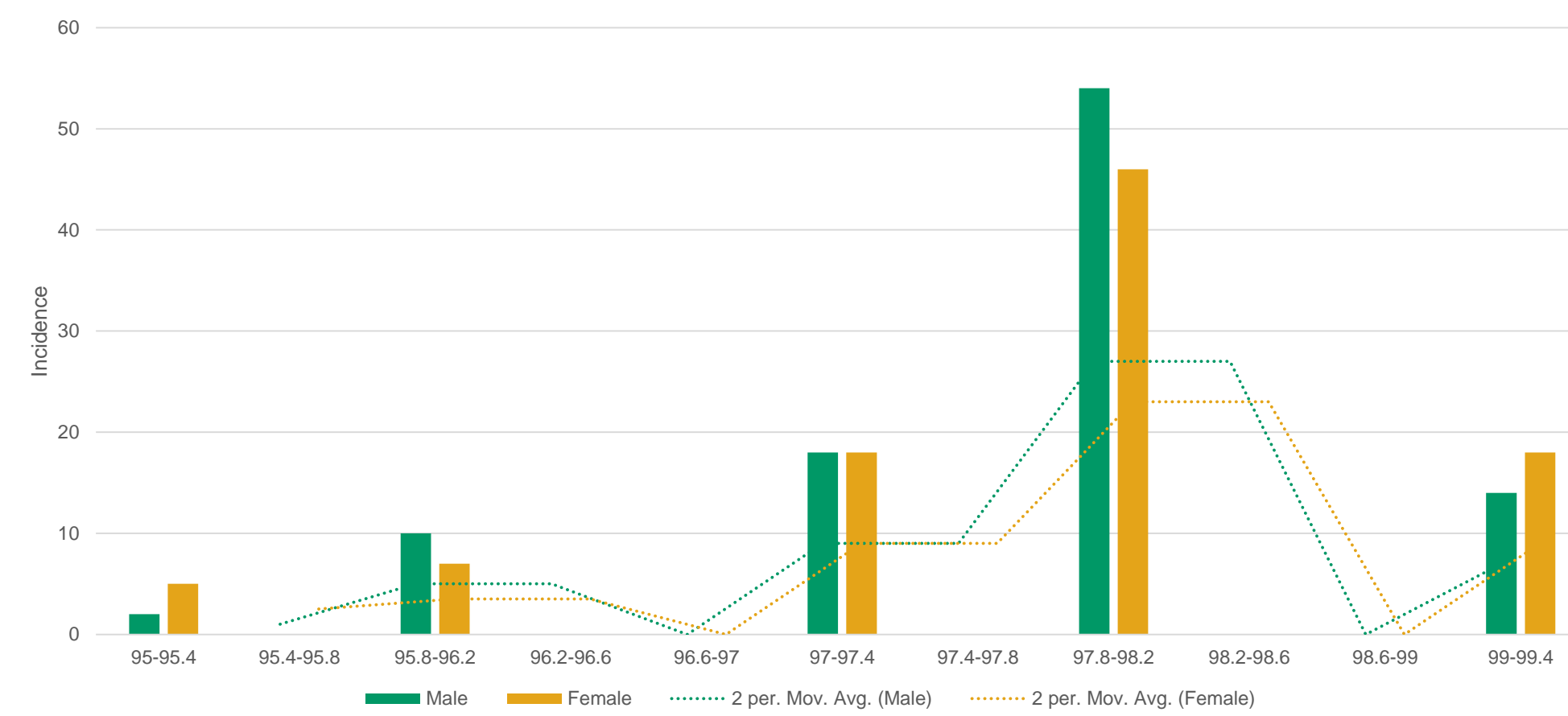
**Table 2. Blood gas parameters obtained from 94 female cynomolgus macaques**

	Average	SD	Min	Max	Percentile 5%	Percentile 95%
S02 (%)	97.7	1.03	95.0	99.0	95.7	99.0
P02 (mmHg)	94.9	10.62	62.0	121	74.6	109
PCO2 (mmHg)	30.9	2.70	19.9	35.6	26.4	35.2
pH	7.47	0.075	7.18	7.58	7.33	7.56
Base Excess (millimoles/liter)	-0.894	5.5072	-21.0	9.0	-10.0	6.0
HCO3 (millimoles/liter)	22.8	4.37	7.40	31.30	15.3	28.8
TCO2 (millimoles/liter)	23.7	4.44	8.00	32.00	16.0	30.0

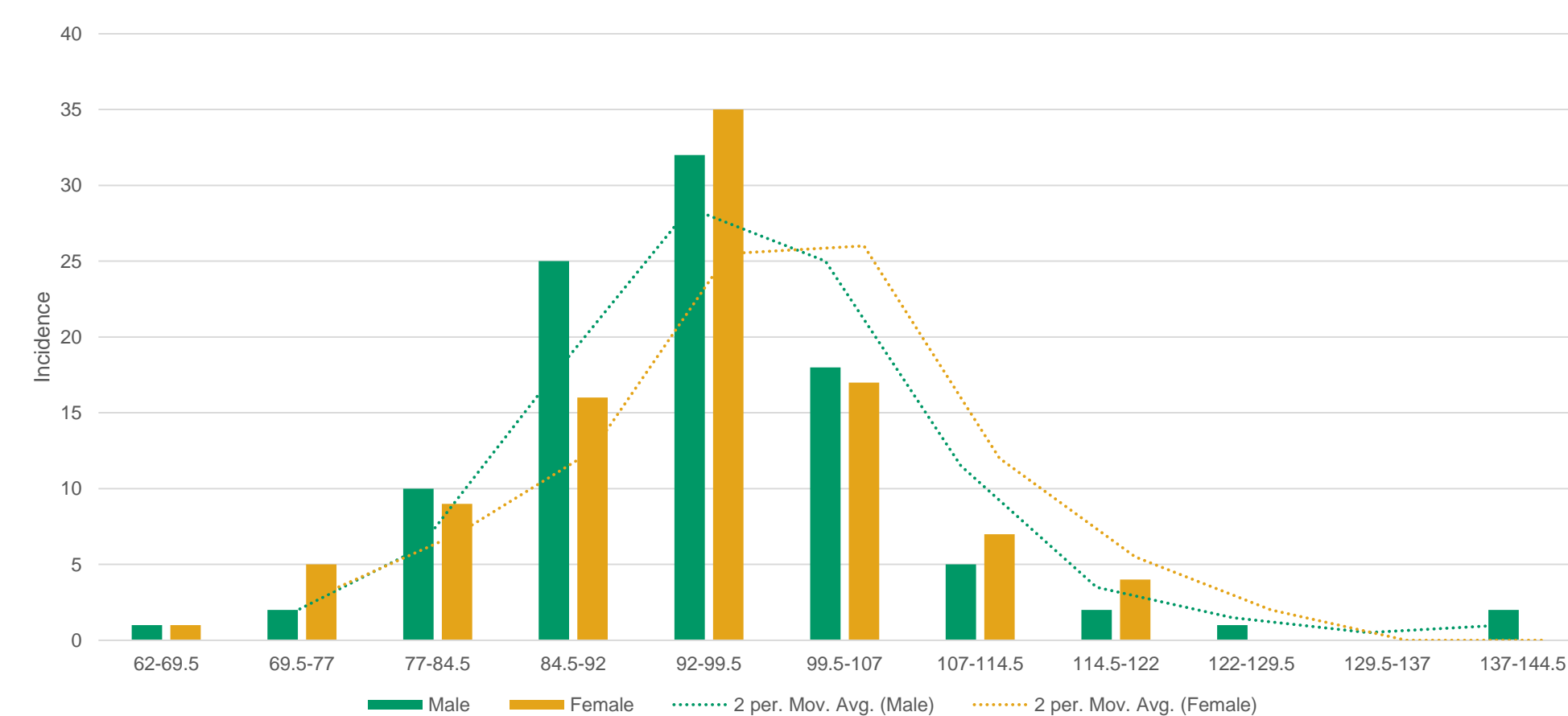
**Table 3. Blood gas parameters obtained from male and female cynomolgus macaques combined**

	Average	SD	Min	Max	Percentile 5%	Percentile 95%
S02	97.7	0.97	95.0	99.0	96.0	99.0
P02	94.9	11.07	62.0	142.0	77.0	110
PCO2 <sup>a</sup>	31.6	3.05	19.9	40.4	26.9	36.0
pH	7.46	0.073	7.17	7.58	7.33	7.56
Base Excess	-0.641	5.6209	-21.0	9.00	-10.5	7.0
HCO3	23.1	4.55	7.40	31.3	15.3	29.7
TCO2	24.0	4.60	8.00	32.0	16.0	31.0

<sup>a</sup> p values: 0.004 (t-test)

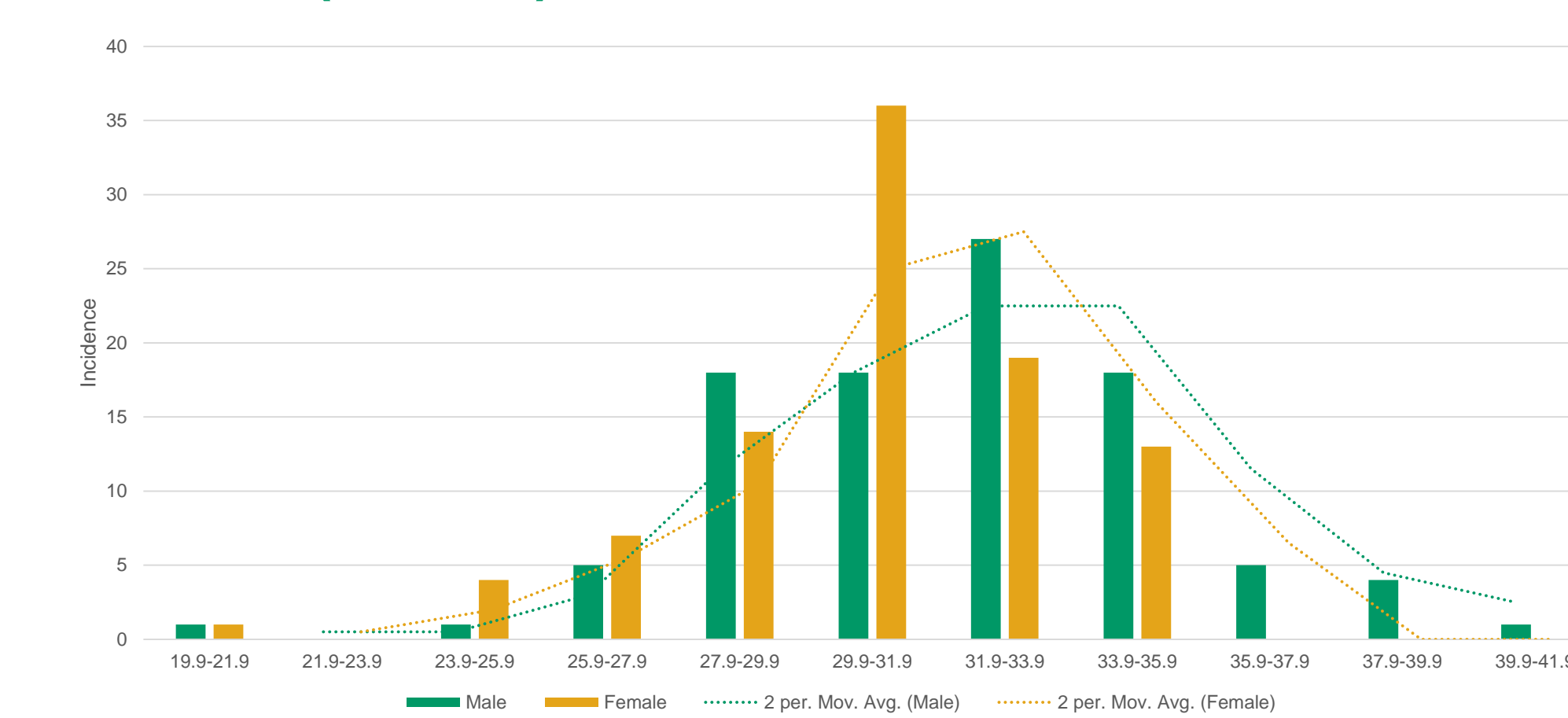


**Figure 1. Saturation in O<sub>2</sub> distribution**

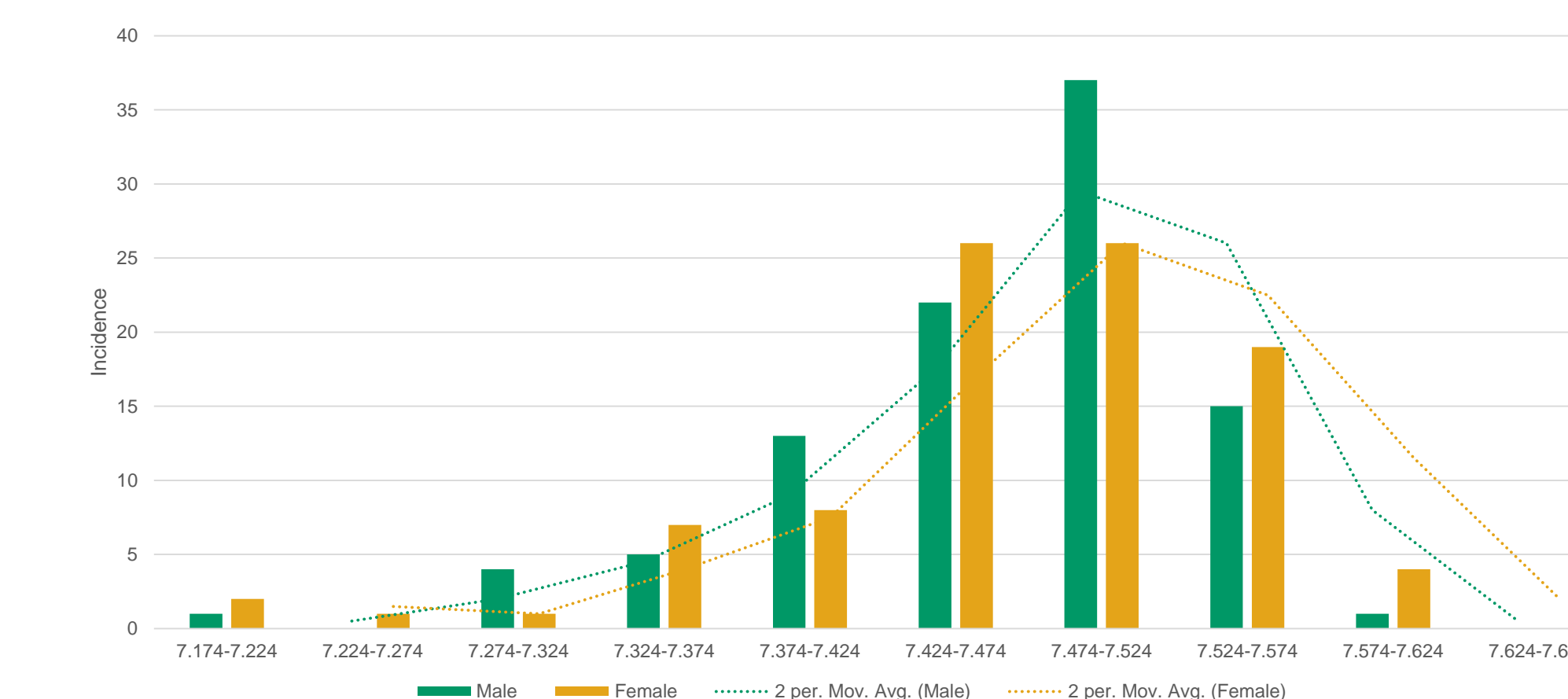


**Figure 2. Partial pressure in O<sub>2</sub> distribution**

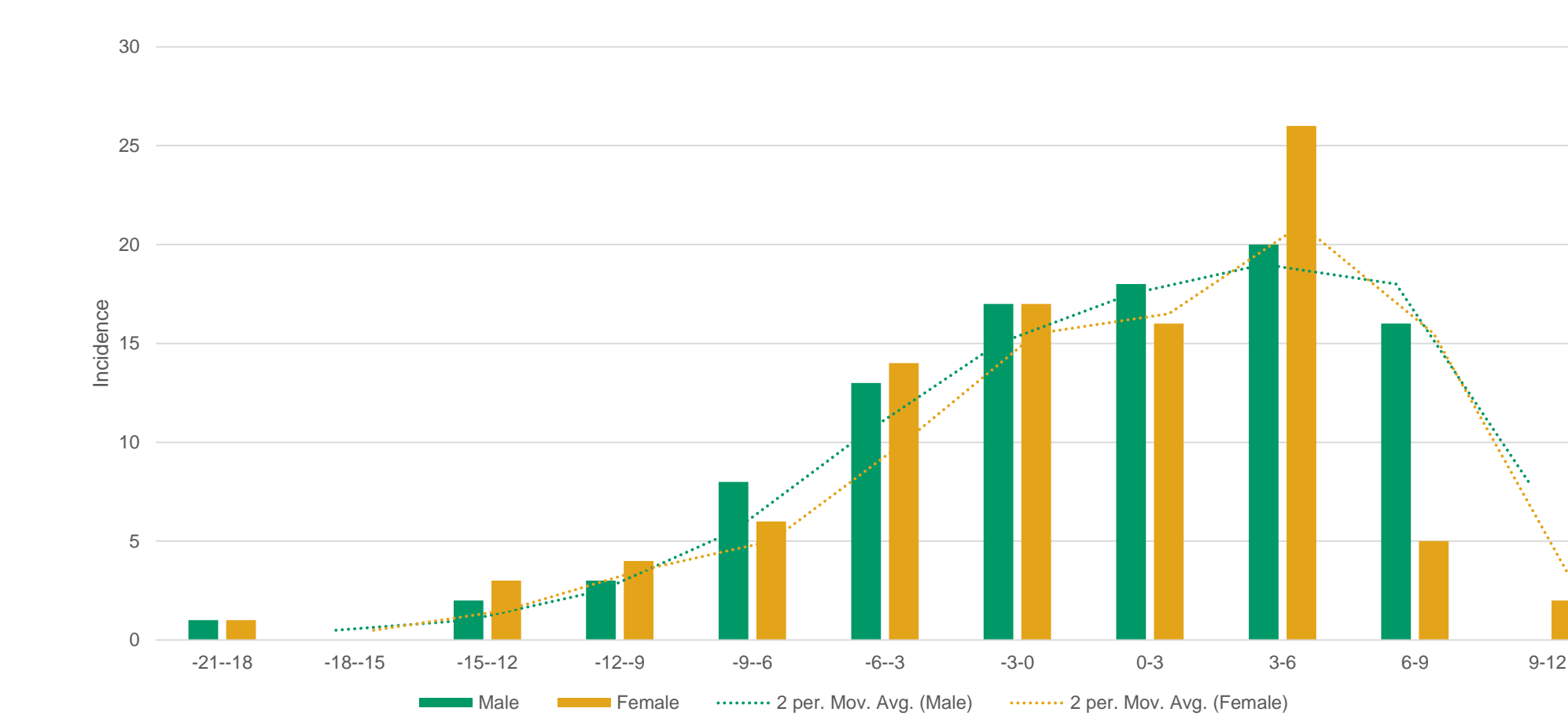
## Results (cont'd)



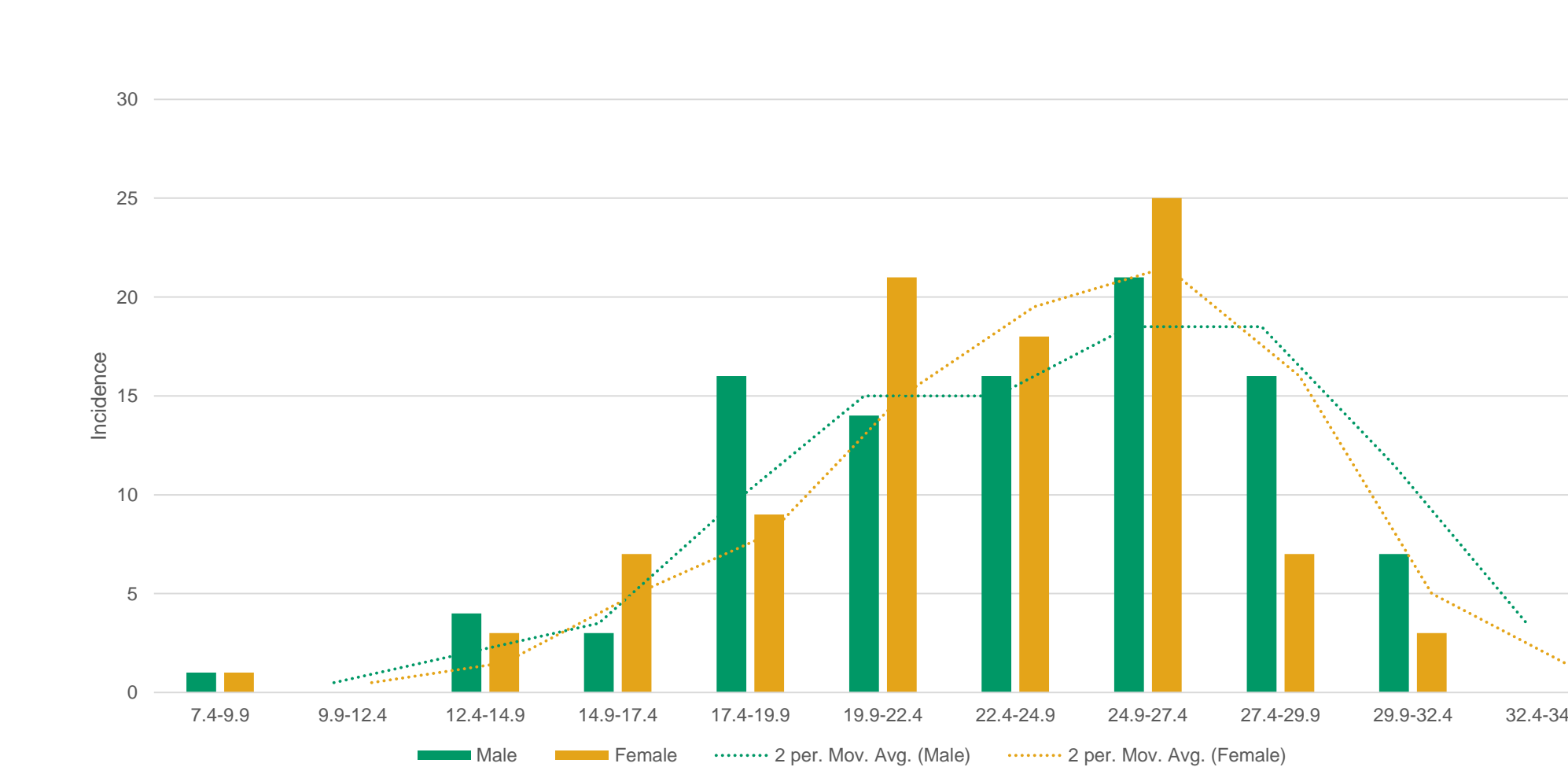
**Figure 3. Partial pressure in CO<sub>2</sub> distribution**



**Figure 4. pH distribution**

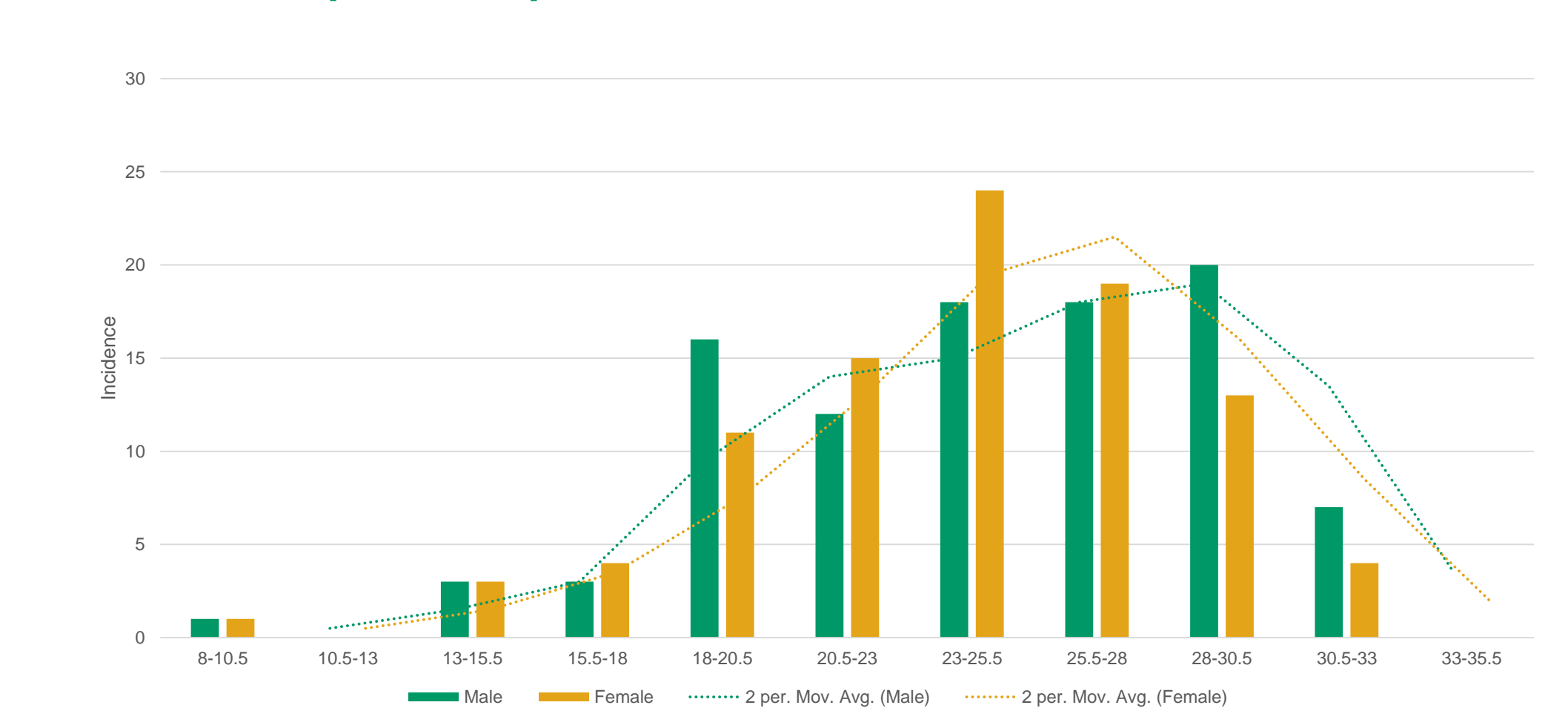


**Figure 5. Base excess distribution**



**Figure 6. Bicarbonate distribution**

## Results (cont'd)



**Figure 7. Total CO<sub>2</sub> distribution**

## Conclusion

The statistical evaluation demonstrated equivalence between male and female animals for data obtained with the exception of the pCO<sub>2</sub>, where mean data were statistically different (p<0.01). After review of the data distribution and trend within the data sets, the difference obtained in pCO<sub>2</sub> was not biologically relevant; therefore, a sex-combined range for all parameters was established.