APPENDICES

APPENDIX 1 - LIST OF FIGURES

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APPENDIX 2 - LIST OF TABLES (contd.)

APPENDIX 3 - GAMMA RADIOLABELLING

Appendix 3.1 Technetium

The majority of the labelling work in this study used the radionuclide Technetium-99m, and this appendix describes the preparation of Technetium-99m from a generator, and the basic chemical reactions involved in the reduction and complexation processes employed in the labelling of aerosol formulations.

Technetium-99m (^{99m}Tc) is conveniently available by elution of a generator containing its parent, Molybdenum-99 (^{99}Mo) (physical half-life 67 hours). A simplifed radioactive decay scheme for ^{99}Mo and ^{99m}Tc is shown in Fig. 3.1.1. ^{99m}Tc is a metastable isotope which is a long-lived excited state of ^{99}Tc, the penultimate decay product of ^{99}Mo. This means that ^{99m}Tc emits gamma radiation only, and the combination of short half-life (6 hours) and lack of non-penetrating (α or β) radiation makes ^{99m}Tc an ideal isotope for nuclear medicine and research.

^{99}Mo is prepared as a fission product or by simple activation of a stable molybdenum oxide target in a high-flux reactor. In the technetium generator, the parent molybdenum is prepared as ammonium molybdate $(NH_4)^+ (MoO_4)^-$ and adsorbed on alumina contained in a glass or plastic column. (Fig. 3.1.2). The ^{99}Mo decays and ^{99m}Tc is formed as the pertechnetate ion $(TcO_4)^-$. When a saline solution is passed through the column the chloride ions exchange with the $(TcO_4)^-$ but not the $(MoO_4)^-$ ions. After passing through the column the saline solution contains sodium pertechnetate $[Na^+(^{99m}TcO_4)^-]$. For practical purposes the eluate is a carrier-free preparation of ^{99m}Tc, and 10 millicuries represent a quantity of only about 1.9 nanograms.

The pertechnetate ion (TcO_4^-) has a similar ionic radius and charge to the iodide ion (I-), and shows a similar biological

Fig 3.1.1. Simplified Radioactive decay scheme of ^{99} Molybdenum and ^{99m}Technetium.

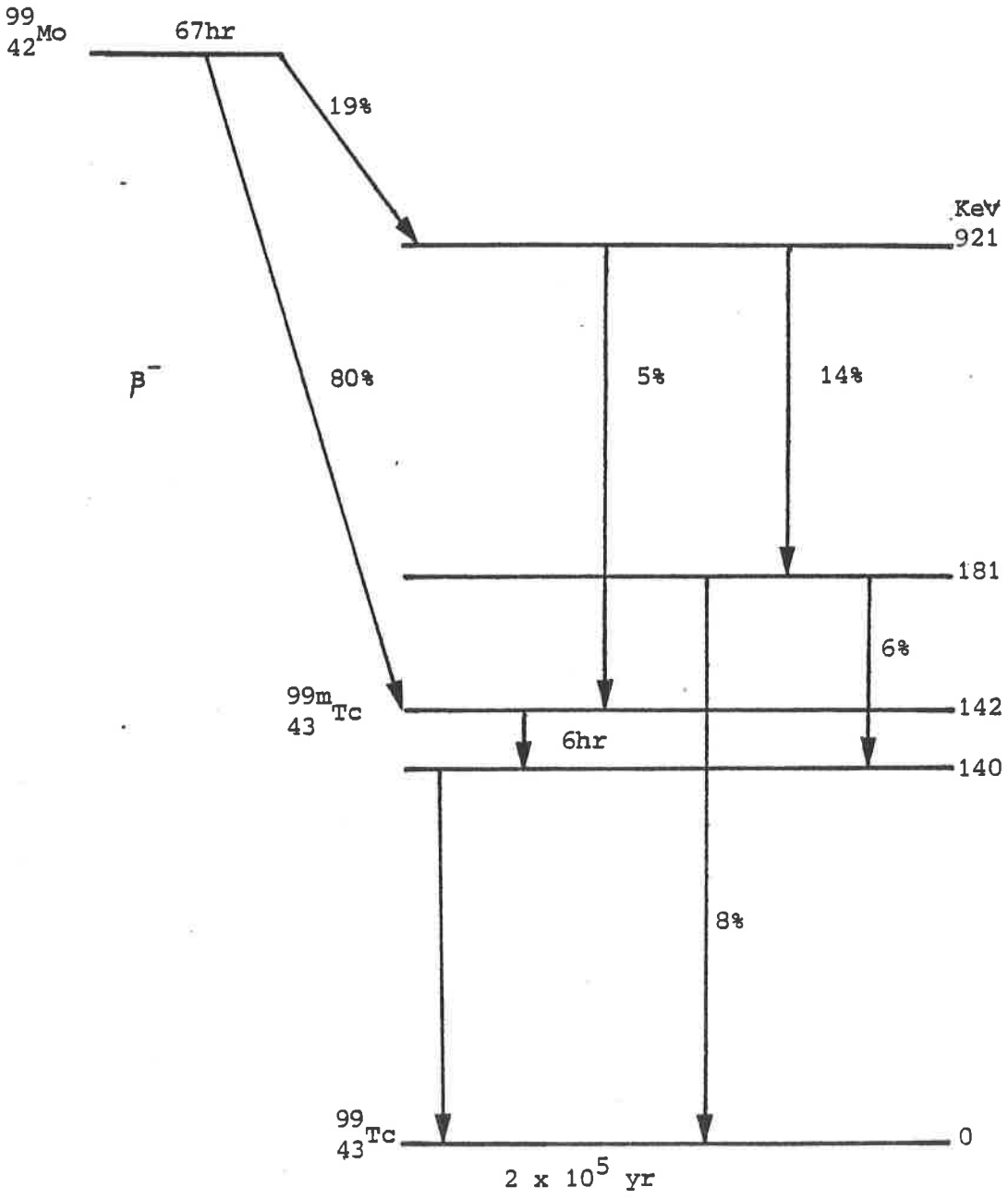
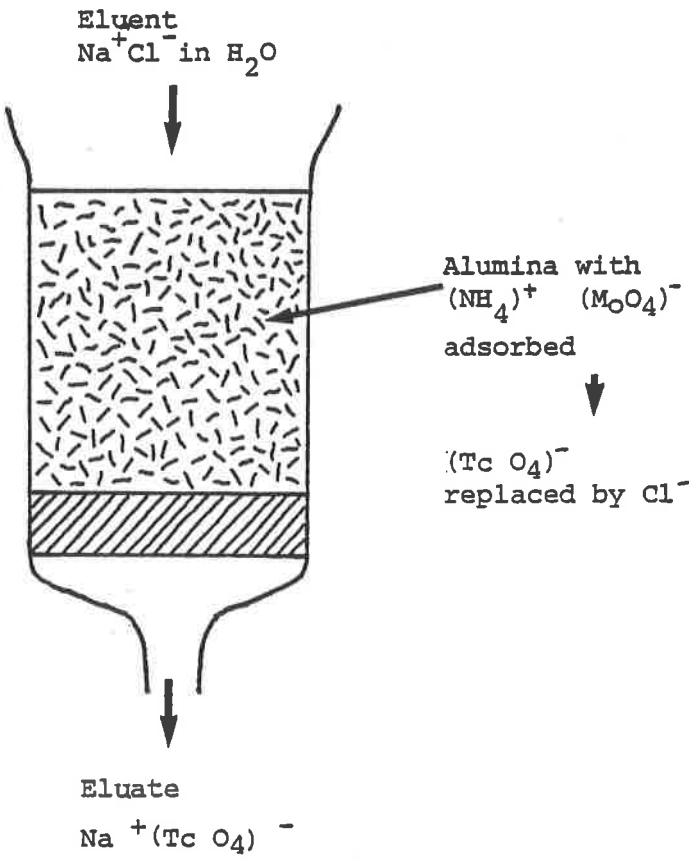


Fig 3.1.2. A Technetium generator.



$$^{99}Mo \xrightarrow[67\ hr]{\beta-} {}^{99m}Tc \xrightarrow[6\ hr]{IT} {}^{99}Tc.$$

distribution to iodide with concentration in the thyroid, salivary glands, choroid plexus and stomach. The ion is readily eliminated by the kidneys, and a large fraction of an orally administered dose is excreted in the faeces since it is only partially absorbed from the gastrointestinal tract.

Technetium is a transition metal (atomic number 43) and most closely resembles rhenium chemically. The outer two valency shells in the electronic configuration contain seven electrons and compounds of technetium are known with oxidation (or valency) states ranging from +7 to -1. The most stable valency states in aqueous media are +7 and +4, whereas valency states of +2, +3, +5, and +6 are unstable and difficult to obtain. Chemically, pertechnetate ($^{99m}TcO_4^-$) is a rather unreactive species and does not label any compound by direct addition. Radiopharmaceutical chemistry involves the reduction of the pertechnetate ion to one or more of the possible lower oxidation states between +6 and +3. Reduction and complex formation depend on at least the following parameters:

1) Redox potentials of the Tc state produced and of the the reducing agent.

2) Concentration of reducing agent, complexing agent, and Tc.

3) Complex stability - ability to hold onto the Tc.

4) Time after production and temperature.

5) Order of adding reagents.

Stannous ion (Sn^{2+}) is the most popular reducing agent:

$$2TcO_4^- + 16H^+ + 3Sn^{2+} \longrightarrow 2Tc(IV)^{4+} + 3Sn^{4+} + 8H_2O.$$

This reaction is reversible and will not keep the Tc reduced to the (IV) state unless it is stablised by the addition of a complexing agent. Fig. 3.1.3 shows a selection of possible complexing agents for reduced technetium.

Fig. 3.1.3 Suitable complexing agents for reduced technetium

anions	- Cl^-, F^-, OH^-
molecules	- H_2O, ROH (alcohols), CO
groups	- amines, sulph hydryl (-SH)
chelates	- DTPA (diethylenetriamine pentaacetic acid)
	- EDTA
proteins	- denatured serum albumin

Appendix 3.2 Specification for Priolene 6952.

Priolene 6952

Cloud point °C	2.0 - 8.0
Iodine value	85 - 93
Acid value	196 - 202
Saponification value	198 - 204
Colour (5-1/4" Lovibond)	7.0Y 1.2R max.
Unsaponifiables	1.0 max.

Typical Composition

C12	Trace	(lauric)
C14	(4.0%	(myristic)
C14.1	(1.5%	(myristoleic)
C16	(4.0%	(palmitic)
C16.1	(8.0%	(palmitoleic)
C17	Trace	(heptadecanoic)
C18	(1.0%	(stearic)
C18.1	(73.5%	(oleic)
C18.2	(6.0%	(linoleic)
C18.3	(Trace	(linoleic)
C20	-	(arachidic)
C20.1	1.0%	(eicosenoic)

Appendix 3.3 (1) Preparation of salbutamol Hemiselenate

1) A solution of selenic acid in water (2.0368g, 14.047 mMol in 10ml solution) was prepared and added to salbutamol base (6.4016g, 26.78 mMol).

2) The mixture was stirred to give a slightly cloudy solution and then absolute alchol (65ml) was added; the product began to crystallise after a few minutes. The mixture was allowed to stand at room temperature overnight.

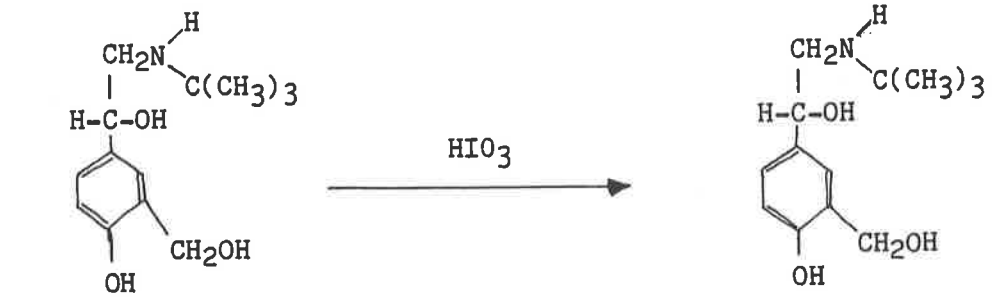
3) The white crystalline product was filtered off and washed with ethanol.

4) After drying in vacuo at 50°C the product was obtained as a white powder.

Yield 7.5946g, 24.38 mMol, 91%.

2) Preparation of salbutamol Iodate

'-[[(1,1-Dimethylethyl)amino]methyl]-4-hydroxybenzenedimethanol. Iodate (II) (Salbutamol Iodate)



$C_{13}H_{21}NO_3$
(239)
(I)

$C_{13}H_{21}NO_3.HIO_3$
(415)
(II)

Appendix 3.4 Andersen Sampler Results from Cocrystallization, chelation and salt formation experiments.

Table 3.4.1 Cocrystallization using Indium oxine (section 3.4.2.2). Data for log-probability graphs Fig. 3.18.

Table 3.4.2 Chelation using Technetium oxine. Method A (section 3.4.2.3). Data for log-probability graphs. Fig. 3.19.

Table 3.4.3 Chelation using Technetium oxine. Method B (section 3.4.2.3). Data for log-probability graphs Fig. 3.20.

Table 3.4.4 Chelation using Technetium oxine. Placebo. (section 3.4.2.3). Data for log-probability graphs. Fig. 3.21.

Table 3.4.5 Chelation using DTPA. Methods A and B (section 3.4.2.3). Data for log-probability graphs Fig. 3.22.

Table 3.4.6 Salt formation using Tc/salbutamol sulphate (section 3.4.2.4). Data for log-probability graphs. Fig. 3.23.

Table 3.4.1 Size distribution data for Fig. 3.18.

Sample	Activity distribution					Drug distribution			
	counts in 600 secs.	corrected counts	%	%-T	cumulative % undersize	µg salbutamol	%-T	cumulative % undersize
Can 1								
Throat (T)	31655	31655	45.0			700.4		
0	1271	1367	1.9	3.5	96.5	36.3	3.6	96.2
1	1360	1581	2.2	4.1	92.4	43.2	4.2	92.0
2	1447	1809	2.6	4.7	87.7	57.1	5.6	86.4
3	4155	5504	7.9	14.3	73.4	221.7	21.8	64.6
4	6671	9668	13.7	25.0	48.4	278.8	27.4	37.2
5	7015	10961	15.6	28.3	20.1	278.3	27.4	9.8
6	1891	3152	4.5	8.1	12.0	70.4	6.9	2.9
7	1525	2723	3.9	7.0	5.0	22.9	2.2	0.7
8 (Filter)	1004	1931	2.7	5.0		6.9	0.7	
Can 2								
Throat (T)	18514	39391	37.3			701.1		
0	1160	2607	2.5	3.9	95.9	30.7	3.0	97.0
1	1173	2826	2.7	4.3	91.6	40.5	4.0	93.0
2	1181	3067	2.9	4.6	87.0	54.2	5.3	87.7
3	3010	8361	7.9	12.6	74.4	216.7	21.3	66.4
4	5103	15232	14.4	23.0	51.4	280.2	27.5	38.9
5	6071	19584	18.5	29.5	21.9	277.8	27.3	11.6
6	1760	6069	5.7	9.1	12.8	87.0	8.5	3.1
7	1262	4674	4.4	7.0	5.8	17.1	1.7	1.4
8 (Filter)	971	3884	3.7	5.8		13.9	1.4	

Table 3.4.2 Size distribution data for Fig. 3.19

Sample	counts	% -T	cumulative % undersize	µg salbutamol	% -T	cumulative % undersize
Can 1						
Throat (T)	193924			234.0		
0	1890	1.0	98.9	1.1	0.5	99.6
1	1905	1.0	97.9	1.1	0.5	99.1
2	2194	1.2	96.7	1.2	0.6	98.5
3	12204	6.6	90.1	6.3	2.9	95.6
4	45904	24.7	65.4	59.0	26.7	68.9
5	62000	33.4	32.0	105.4	47.7	21.2
6	35027	18.9	13.1	40.8	18.5	2.7
7	13064	7.0	6.1	4.6	2.1	0.6
8 Filter	11317	6.1		1.5	0.6	
Can 2						
Throat (T)	221320			294.5		
0	1112	0.6	99.2	1.1	0.5	99.4
1	1290	0.7	98.5	1.0	0.4	99.0
2	1736	1.0	97.5	1.1	0.5	98.5
3	8430	4.7	92.8	5.0	2.2	96.3
4	36915	20.8	72.0	56.8	25.1	71.2
5	72875	41.1	30.9	109.1	48.3	22.9
6	31812	17.9	13.0	45.0	19.9	3.0
7	12260	6.9	6.1	5.2	2.3	0.7
8 Filter	10904	6.1		1.6	0.7	
Can 3						
Throat (T)	30767			274.0		
0	160	0.6	99.1	0.7	0.3	99.5
1	202	0.8	98.3	0.6	0.3	99.2
2	222	0.9	97.4	0.7	0.3	98.9
3	1013	4.1	93.3	4.1	2.0	96.9
4	4676	19.1	74.2	45.0	21.5	75.4
5	10660	43.6	30.6	111.4	53.3	22.1
6	4203	17.2	13.4	40.4	19.3	2.8
7	1551	6.3	7.1	4.5	2.1	0.7
8 Filter	1731	7.1		1.5	0.7	
Can 4						
Throat (T)	28370			261.0		
0	146	0.7	99.2	0.7	0.3	99.7
1	185	0.8	98.4	0.7	0.3	99.4
2	202	0.9	97.5	0.8	0.3	99.1
3	862	3.9	93.6	3.6	1.5	97.6
4	4066	18.7	74.9	93.8	38.3	59.3
5	9431	43.3	31.6	102.8	41.9	17.4
6	3774	17.3	14.3	37.0	15.1	2.3
7	1501	6.9	7.4	4.2	1.7	0.6
8 Filter	1610	7.4		1.5	0.6	

Table 3.4.3 Size distribution data for Fig. 3.20

Sample	counts	% -T	cumulative % undersize	µg salbutamol	% -T	cumulative % undersize
Can 1						
Throat (T)	174064			228.0		
0	2140	2.2	97.7	1.3	1.7	98.2
1	4425	4.6	93.1	2.1	2.8	95.4
2	5112	5.3	87.8	2.8	3.7	91.7
3	14330	14.8	73.0	9.0	12.1	79.6
4	23157	24.0	49.0	38.1	51.7	27.9
5	25336	26.2	22.8	16.5	22.4	5.5
6	9820	10.2	12.6	2.8	3.7	1.8
7	6754	7.0	5.6	0.9	1.2	0.6
8 Filter	5430	5.6		0.4	0.6	
Can 2						
Throat (T)	143403			192.0		
0	3037	3.3	96.5	2.2	6.1	94.8
1	6264	6.8	89.7	3.1	7.3	87.5
2	6166	6.7	83.0	3.5	8.2	79.3
3	14800	16.1	66.9	9.8	22.8	56.5
4	19330	21.0	45.9	15.9	37.1	19.4
5	21277	23.1	22.8	6.3	14.7	4.7
6	8342	9.1	13.7	0.7	1.7	3.0
7	6195	6.7	7.0	0.6	1.4	1.6
8 Filter	6485	7.0		0.7	1.6	

Table 3.4.4 Size distribution data for Fig. 3.21

Sample	counts	%	% -T	cumulative % undersize
Can 1				
Throat (T)	10149	51.7		
0	71	0.4	0.7	99.2
1	38	0.2	0.4	98.8
2	45	0.2	0.5	98.3
3	47	0.2	0.5	97.8
4	291	1.5	3.1	94.7
5	2378	12.1	25.1	69.6
6	2860	14.6	30.1	39.5
7	2092	10.6	22.0	17.5
8 Filter	1662	8.5	17.5	
Can 2				
Throat (T)	9996	55.5		
0	20	0.1	0.2	99.7
1	41	0.2	0.5	99.2
2	37	0.2	0.5	98.7
3	46	0.2	0.6	98.1
4	152	0.8	1.9	96.2
5	1908	10.6	23.8	72.4
6	2489	13.8	31.1	41.3
7	1915	10.6	23.9	17.4
8 Filter	1392	7.7	17.4	

Table 3.4.5 Size distribution data for Fig. 3.22

Sample	counts	% -T	cumulative % undersize	µg salbutamol	% -T	cumulative % undersize
Method A						
Throat (T)	180767			240.0		
0	3066	8.1	91.8	5.7	3.9	96.0
1	1110	2.9	88.9	9.0	6.2	89.8
2	759	2.0	86.9	8.0	5.5	84.3
3	2505	6.6	80.3	11.3	7.8	76.5
4	6032	16.0	64.3	19.3	13.3	63.2
5	13429	35.5	28.8	26.3	18.1	45.1
6	5302	14.0	14.8	16.2	11.2	33.9
7	1510	4.0	10.8	15.0	10.3	23.6
8 Filter	4081	10.8		34.2	23.6	
Method B	($\times 10^4$)					
Throat (T)	474			282.1		
0	4.47	2.6	97.3	22.9	7.8	93.3
1	4.27	2.5	94.8	24.8	8.4	84.9
2	4.43	2.6	92.2	23.5	8.0	76.9
3	13.89	8.2	84.0	35.3	12.0	64.9
4	28.40	16.7	67.3	45.6	15.5	49.4
5	44.50	26.2	41.1	66.3	22.5	26.9
6	27.70	16.3	24.8	11.3	3.8	23.1
7	16.39	9.6	15.2	7.0	2.4	20.7
8 Filter	25.86	15.2		60.8	20.7	

Table 3.4.6 Size distribution data for Fig. 3.23

Sample	counts	% -T&P	cumulative % undersize	µg salbutamol	% -T&P	cumulative % undersize
Throat (T)	276927			398.1		
Preseparator (P)	70446			95.0		
0	4191	0.4	99.5	10.4	0.6	99.2
1	3980	0.4	99.1	9.3	0.5	98.7
2	4207	0.4	98.7	11.7	0.7	98.0
3	27841	2.5	96.2	44.6	2.6	95.4
4	227083	20.8	75.4	348.4	20.1	75.3
5	411540	37.6	37.8	766.4	44.3	31.0
6	142710	13.0	24.8	281.0	16.2	14.8
7	91159	8.3	16.5	139.0	8.0	6.8
8 Filter	180844	16.5		118.2	6.8	

Appendix 3.5. Andersen Sampler Results from experiments using Tc-Ph_4AsCl complex (see section 3.4.3.4)

Table 3.5.1 Initial experiments (Fig. 3.24).

Table 3.5.2 Experiment (a) concentration of Ph_4AsCl and mbk in labelled complex solution (Fig. 3.25).

Table 3.5.3 Experiment (b) amount of shaking during separation and temperature of water-bath (Fig. 3.26).

Table 3.5.4 Experiment (c) and (d) order of addition of components and dose/shot, number of shots (Fig. 3.27).

Table 3.5.5 as Table 3.10.4 (Fig. 3.28).

Table 3.5.6 effect of solvent, mbk, alone (Fig. 3.29).

Table 3.5.7 effect of oleic acid in formulation (Fig. 3.30).

Table 3.5.8 time interval between manufacture and sampling (Fig. 3.31).

Table 3.5.9 reproducibility of results - 3 cans from same batch (Fig. 3.32).

Table 3.5.10 reproducibility of results - within 1 can and assay method (Fig. 3.33).

Table 3.5.11 Placebo MDI's (Fig. 3.34).

Table 3.5.1 Size distribution data for Fig. 3.24

Sample	counts	% -T	cumulative % undersize	µg salbutamol	% -T	cumulative % undersize
Can 1						
Throat (T)	46387			805.4		
0	1800	4.4	95.5	25.1	1.6	98.3
1	985	2.4	93.1	9.8	0.6	97.7
2	676	1.7	91.4	33.4	2.2	95.5
3	3783	9.3	82.1	167.7	11.0	84.5
4	11700	28.9	53.2	467.6	30.6	53.9
5	16666	41.2	12.0	622.4	40.8	13.1
6	3666	9.1	2.9	166.7	10.9	2.2
7	723	1.8	1.1	22.4	1.5	0.7
8 Filter	450	1.1		10.2	0.7	
Can 2						
Throat (T)	53587			1556.5		
0	2910	7.3	92.6	32.2	2.2	97.7
1	1060	2.6	90.0	36.8	2.5	95.2
2	964	2.4	87.6	38.8	2.6	92.6
3	5001	12.5	75.1	182.3	12.4	80.2
4	11726	29.3	45.8	438.1	29.9	50.3
5	14196	35.5	10.3	565.3	38.6	11.7
6	3006	7.5	2.8	134.7	9.2	2.5
7	810	2.0	0.8	27.6	1.9	0.6
8 Filter	323	0.8		8.8	0.6	
Can 3						
Throat (T)	459935			622.0		
0	12282	4.0	95.9	16.8	1.4	98.5
1	4052	1.3	94.6	18.0	1.5	97.0
2	4364	1.4	93.2	17.6	1.5	95.5
3	16622	5.4	87.8	71.2	5.9	89.6
4	68300	22.4	65.4	273.0	22.5	67.1
5	141106	46.2	19.2	577.6	47.6	19.5
6	43164	14.1	5.1	182.4	15.0	4.5
7	9168	3.0	2.1	42.8	3.5	1.0
8 Filter	6310	2.1		12.8	1.0	
Can 4						
Throat (T)	648510			866.0		
0	11378	3.6	96.0	21.2	2.0	98.0
1	5038	1.6	94.4	16.0	1.5	96.5
2	5380	1.7	92.7	17.2	1.6	94.9
3	24270	7.8	84.9	96.8	9.1	85.8
4	76466	24.7	60.2	316.0	29.7	56.1
5	133093	43.0	17.2	421.0	39.6	16.5
6	38158	12.3	4.9	136.0	12.8	3.7
7	8428	2.7	2.2	25.2	2.4	1.3
8 Filter	6954	2.2		14.0	1.3	

Table 3.5.2 Size distribution data for Fig. 3.25

Sample	counts	% -T	cumulative % undersize	µg salbutamol	% -T	cumulative % undersize
Can 1	x10-3					
Throat (T)	2469.1			1187.9		
0	31.0	1.7	98.3	11.7	1.5	98.6
1	61.7	3.3	95.0	21.4	2.8	95.8
2	136.2	7.3	87.7	46.4	6.1	89.7
3	621.1	33.4	54.3	242.8	31.9	57.8
4	604.5	32.5	21.8	278.0	36.5	21.3
5	267.7	14.4	7.4	124.7	16.4	4.9
6	73.3	3.9	3.5	21.9	2.9	2.0
7	28.1	1.5	2.0	5.0	0.7	1.3
8 Filter	37.3	2.0		9.9	1.3	
Can 2						
Throat (T)	1637.1			1327.7		
0	16.4	1.9	98.3	5.4	2.0	97.9
1	16.7	1.9	96.4	5.4	2.0	95.9
2	17.2	2.0	94.4	8.4	3.1	92.8
3	86.5	10.0	84.4	57.0	21.3	71.5
4	232.2	26.8	57.6	67.1	25.1	46.4
5	362.4	41.8	15.8	103.8	38.8	7.6
6	64.7	7.5	8.3	9.6	3.6	4.0
7	19.3	2.2	6.1	4.2	1.6	2.4
8 Filter	52.6	6.1		6.4	2.4	
Can 3	x10-2					
Throat (T)	4117.0			1136.2		
0	78.5	6.2	93.9	18.5	2.7	97.2
1	66.9	5.3	88.6	16.1	2.4	94.8
2	96.0	7.6	81.0	24.3	3.6	91.2
3	272.2	21.4	59.6	268.1	39.7	51.5
4	364.6	28.7	30.9	156.8	23.2	28.3
5	240.9	19.0	11.9	157.0	23.2	5.1
6	75.0	5.9	6.0	19.7	2.9	2.2
7	38.3	3.0	3.0	5.5	0.8	1.4
8 Filter	38.5	3.0		9.6	1.4	
Can 4						
Throat (T)	10416.7			1335.2		
0	62.8	2.8	97.3	7.9	4.5	95.5
1	42.1	1.9	95.4	5.5	3.1	92.4
2	65.4	3.0	92.4	10.0	5.6	86.8
3	317.4	14.4	78.0	49.7	28.1	58.7
4	600.6	27.2	50.8	37.6	21.2	37.5
5	793.9	36.0	14.8	48.3	27.3	10.2
6	101.6	4.6	10.2	7.9	4.5	5.7
7	41.4	1.9	8.3	3.2	1.8	3.9
8 Filter	181.4	8.3		7.0	3.9	

Table 3.5.3 Size distribution data for Fig. 3.26

Sample	counts	% -T	cumulative % undersize	µg salbutamol	% -T	cumulative % undersize
Can 1	x10-2					
Throat (T)	946.5			307.2		
0	3.2	0.7	99.2	2.1	0.8	99.2
1	4.5	1.0	98.2	2.6	1.0	98.2
2	6.9	1.6	96.6	3.8	1.4	96.8
3	46.3	10.8	85.8	38.1	14.5	82.3
4	152.4	35.5	50.3	108.1	41.0	41.3
5	165.2	38.4	11.9	92.0	34.9	6.4
6	34.2	7.9	4.0	10.4	3.9	2.5
7	11.1	2.6	1.4	2.1	0.8	1.7
8 Filter	6.0	1.4		4.4	1.7	
Can 2						
Throat (T)	1691.6			253.8		
0	8.9	1.0	99.2	3.9	1.2	98.7
1	17.7	2.0	97.2	4.6	1.4	97.3
2	28.9	3.2	94.0	7.7	2.3	95.0
3	173.8	19.2	74.8	59.9	18.2	76.8
4	352.5	39.0	35.8	141.3	42.8	34.0
5	271.8	30.0	5.8	95.4	28.9	5.1
6	38.0	4.2	1.6	8.4	2.5	2.6
7	8.6	1.0	0.6	1.8	0.5	2.1
8 Filter	4.8	0.6		7.0	2.1	
Can 3						
Throat (T)	866.8			276.3		
0	3.0	0.8	99.1	2.2	0.8	99.3
1	3.4	0.9	98.2	2.2	0.8	98.5
2	5.7	1.5	96.7	4.2	1.4	97.1
3	34.8	9.3	87.4	31.2	10.7	86.4
4	137.0	36.7	50.7	122.6	42.1	44.3
5	143.6	38.5	12.2	105.7	36.3	8.0
6	30.8	8.3	3.9	15.5	5.3	2.7
7	9.0	2.4	1.5	2.4	0.8	1.9
8 Filter	5.5	1.5		5.5	1.9	
Can 4						
Throat (T)	1565.1			265.8		
0	15.5	2.5	97.5	5.1	2.0	98.1
1	14.7	2.4	95.1	4.9	1.9	96.2
2	22.9	3.7	91.4	10.7	4.1	92.1
3	138.7	22.3	69.1	53.1	20.5	71.6
4	253.8	40.8	28.3	106.8	41.2	30.4
5	149.3	24.0	4.3	63.9	24.7	5.7
6	18.1	2.9	1.4	7.0	2.7	3.0
7	4.9	0.8	0.6	2.9	1.1	1.9
8 Filter	4.0	0.6		4.8	1.9	

Table 3.5.4 Size distribution data for Fig. 3.27

Sample	counts	% -T	cumulative % undersize	µg salbutamol	% -T	cumulative % undersize
Can 1	x10-3					
Throat (T)	5882.4			677.4		
0	44.8	0.8	99.2	3.1	1.3	98.7
1	32.9	0.6	98.6	2.5	1.0	97.7
2	63.1	1.2	97.4	4.1	1.7	96.0
3	451.0	8.4	89.0	26.6	11.1	84.9
4	1846.2	34.4	54.6	107.2	44.7	40.2
5	1863.4	34.8	19.8	76.6	32.0	8.2
6	674.9	12.6	7.2	10.0	4.2	4.0
7	240.1	4.5	2.7	2.8	1.2	2.8
8 Filter	145.3	2.7		6.8	2.8	
Can 2						
Throat (T)	3000.0			1040.1		
0	34.2	1.9	98.1	8.9	1.7	98.4
1	39.6	2.2	95.9	10.6	2.0	96.4
2	93.9	5.2	90.7	22.0	4.2	92.2
3	542.7	30.0	60.7	137.6	26.0	66.2
4	714.7	39.6	21.1	225.2	42.6	23.6
5	285.3	15.8	5.3	100.7	19.1	4.5
6	38.6	2.1	3.2	13.5	2.6	1.9
7	16.6	0.9	2.3	4.0	0.8	1.1
8 Filter	40.8	2.3		6.1	1.1	
Can 3	x10-2					
Throat (T)	806.5			1360.1		
0	8.5	2.4	97.5	12.0	1.3	98.6
1	9.4	2.7	94.8	19.9	2.2	96.4
2	12.1	3.5	91.3	38.6	4.2	92.2
3	56.0	16.1	75.2	225.8	24.7	67.5
4	113.1	32.6	42.6	387.1	42.4	25.1
5	107.9	31.1	11.5	189.7	20.8	4.3
6	18.1	5.2	6.3	23.1	2.5	1.8
7	7.4	2.1	4.2	7.9	0.9	0.9
8 Filter	14.7	4.2		8.8	0.9	
Can 4						
Throat (T)	813.2			1593.2		
0	10.8	3.7	96.4	25.2	3.0	97.0
1	9.6	3.3	93.1	26.8	3.2	93.8
2	15.7	5.3	87.8	43.3	5.2	88.6
3	55.8	18.9	68.9	227.6	27.2	61.4
4	95.3	32.3	36.6	340.7	40.7	20.7
5	64.8	22.0	14.6	139.4	16.7	4.0
6	15.8	5.4	9.2	15.9	1.9	2.1
7	6.7	2.3	6.9	5.4	0.6	1.5
8 Filter	20.4	6.9		12.4	1.5	

Table 3.5.5 Size distribution data for Fig. 3.28

Sample	counts	% -T	cumulative % undersize	µg salbutamol	% -T	cumulative % undersize
Can 5	x10-3					
Throat (T)	1550.4			1921.8		
0	18.6	3.9	96.1	28.3	3.3	96.6
1	16.9	3.5	92.6	25.1	2.9	93.7
2	20.5	4.3	88.3	44.7	5.2	88.5
3	104.0	21.6	66.7	242.6	28.3	60.2
4	154.2	32.1	34.6	333.5	38.9	21.3
5	112.7	23.4	11.2	150.1	17.5	3.8
6	20.6	4.3	6.9	15.9	1.9	1.9
7	10.5	2.2	4.7	5.4	0.6	1.3
8 Filter	22.6	4.7		10.9	1.3	
Can 6						
Throat (T)	511.7			1287.5		
0	5.8	1.9	98.2	5.2	0.8	99.2
1	8.0	2.6	95.6	11.4	1.7	97.5
2	16.4	5.3	90.3	30.1	4.4	93.1
3	82.0	26.4	63.9	171.8	25.3	67.8
4	113.3	36.5	27.4	290.3	42.8	25.0
5	56.3	18.1	9.3	138.0	20.3	4.7
6	16.0	5.2	4.1	18.3	2.7	2.0
7	7.7	2.5	1.6	4.0	0.6	1.4
8 Filter	5.1	1.6		9.2	1.4	
Can 7a						
Throat (T)	466.2			1112.8		
0	3.0	1.5	98.6	4.0	0.7	99.3
1	4.2	2.1	96.5	8.3	1.5	97.8
2	7.9	3.9	92.6	17.8	3.2	94.6
3	48.3	23.7	68.9	133.6	24.0	70.6
4	78.0	38.3	30.6	241.1	43.3	27.3
5	42.6	20.9	9.7	117.3	21.1	6.2
6	10.5	5.2	4.5	19.6	3.5	2.7
7	5.4	2.7	1.8	6.2	1.1	1.6
8 Filter	3.6	1.8		8.6	1.6	
Can 7b						
Throat (T)	383.0			1009.4		
0	4.0	1.9	98.2	7.2	1.2	98.8
1	5.3	2.5	95.7	12.3	2.0	96.8
2	12.4	5.9	89.8	29.6	4.9	91.9
3	58.6	27.8	62.0	163.4	27.2	64.7
4	76.8	36.4	25.6	249.8	41.5	23.2
5	37.5	17.8	7.8	104.9	17.4	5.8
6	9.1	4.3	3.5	19.2	3.2	2.6
7	4.0	1.9	1.6	4.8	0.8	1.8
8 Filter	3.4	1.6		10.6	1.8	

Table 3.5.6 Size distribution data for Fig. 3.[29]

Sample	µg salbutamol	%	%-T & A	cumulative % undersize
Actuator	190.2	11.3		
Throat	1078.5	64.0		
0	8.4		2.0	97.9
1	5.2		1.3	96.6
2	8.0		1.9	94.7
3	66.5		16.0	78.7
4	185.0		44.5	34.2
5	122.1		29.4	4.8
6	11.0		2.6	2.2
7	3.7		0.9	1.3
8 Filter	5.4		1.3	

Table 3.5.7 Size distribution data for Fig. 3.30

Sample	counts	% -T	cumulative % undersize	µg salbutamol	% -T	cumulative % undersize
Can 1	x10-3					
Throat (T)	1780.4			921.0		
0	32.9	8.6	91.4	12.5	5.8	94.2
1	22.0	5.7	85.7	10.3	4.8	89.4
2	18.3	4.8	80.9	9.8	4.5	84.9
3	52.6	13.7	67.2	34.6	16.0	68.9
4	137.5	35.9	31.3	55.5	25.7	43.2
5	82.9	21.6	9.7	70.9	32.9	10.3
6	20.5	5.3	4.4	10.9	5.1	5.2
7	7.6	2.0	2.4	3.2	1.5	3.7
8 Filter	9.0	2.4		8.1	3.7	
Can 2						
Throat (T)	851.7			939.5		
0	12.5	4.9	95.2	10.4	4.6	95.3
1	11.0	4.3	90.9	10.1	4.4	90.9
2	10.4	4.1	86.8	11.2	4.9	86.0
3	35.3	13.9	72.9	48.6	21.4	64.6
4	71.0	27.9	45.0	50.8	22.3	42.3
5	68.0	26.7	18.3	77.6	34.1	8.2
6	19.6	7.7	10.6	8.3	3.6	4.6
7	9.0	3.5	7.1	4.4	1.9	2.7
8 Filter	17.9	7.1		6.1	2.7	

Table 3.5.8 Size distribution data for Fig. 3.31

Sample	counts	% -T	cumulative % undersize	µg salbutamol	% -T	cumulative % undersize
	x10^{-2}					
Can 1						
Throat (T)	2197.8			273.3		
0	11.9	1.1	99.1	2.9	1.0	99.0
1	16.0	1.5	97.6	2.8	1.0	98.0
2	36.3	3.3	94.3	7.1	2.5	95.5
3	212.3	19.3	75.0	46.8	16.4	79.1
4	440.4	40.0	35.0	118.0	41.3	37.8
5	317.9	28.9	6.1	89.9	31.5	6.3
6	48.8	4.4	1.7	11.2	3.9	2.4
7	9.5	0.9	0.8	2.8	1.0	1.4
8 Filter	8.0	0.8		4.1	1.4	
Can 2						
Throat (T)	2143.6			272.0		
0	14.0	1.4	98.6	2.9	1.0	98.9
1	32.5	3.3	95.3	3.9	1.4	97.5
2	73.6	7.4	87.9	11.6	4.2	93.3
3	297.2	30.0	57.9	68.2	24.8	68.5
4	333.5	33.7	24.2	102.7	37.3	31.2
5	193.0	19.5	4.7	66.8	24.3	6.9
6	31.5	3.2	1.5	8.8	3.2	3.7
7	7.8	0.8	0.7	1.8	0.7	3.0
8 Filter	7.1	0.7		8.3	3.0	
Can 3						
Throat (T)	2509.4			298.7		
0	91.5	5.9	94.1	1.5	0.7	99.2
1	131.5	8.5	85.6	6.2	2.7	96.5
2	145.2	9.3	76.3	15.0	6.6	89.9
3	302.7	19.5	56.8	53.6	23.7	66.2
4	296.1	19.0	37.8	70.7	31.2	35.0
5	217.7	14.0	23.8	44.5	19.7	15.3
6	110.8	7.1	16.7	10.5	4.6	10.7
7	95.0	6.1	10.6	6.8	3.0	7.7
8 Filter	165.7	10.6		17.5	7.7	

Table 3.5.9 Size distribution data for Fig. 3.32

Sample	counts	% -T	cumulative % undersize	µg salbutamol	% -T	cumulative % undersize
Can 1	x10-2					
Throat (T)	1369.6			348.1		
0	6.2	0.6	99.4	4.0	1.2	98.7
1	6.4	0.7	98.7	4.5	1.4	97.3
2	11.1	1.2	97.5	7.1	2.1	95.2
3	123.2	12.9	84.6	51.1	15.4	79.8
4	402.4	42.2	42.4	134.6	40.6	39.2
5	339.8	35.6	6.8	93.0	28.1	11.1
6	36.1	3.8	3.0	14.6	4.4	6.7
7	13.9	1.5	1.5	13.4	4.0	2.7
8 Filter	14.8	1.5		9.2	2.7	
Can 2						
Throat (T)	571.0			321.8		
0	4.0	1.6	98.4	4.1	1.5	98.5
1	2.3	0.9	97.5	2.0	0.7	97.8
2	4.5	1.8	95.7	2.6	1.0	96.8
3	19.2	7.5	88.2	33.4	12.2	84.6
4	72.5	28.5	59.7	115.5	42.2	42.4
5	94.9	37.3	22.4	93.5	34.2	8.2
6	39.1	15.4	7.0	13.9	5.1	3.1
7	15.1	5.9	1.1	3.3	1.2	1.9
8 Filter	2.9	1.1		5.2	1.9	
Can 3						
Throat (T)	423.4			327.7		
0	3.4	1.1	98.8	2.6	0.9	99.1
1	2.8	0.9	97.9	2.4	0.8	98.3
2	4.5	1.4	96.5	5.0	1.7	96.6
3	28.6	9.1	87.4	37.2	12.9	83.7
4	121.2	38.4	49.0	123.7	42.8	40.9
5	108.5	34.4	14.6	90.1	31.1	9.8
6	33.1	10.5	4.1	16.8	5.8	4.0
7	7.7	2.4	1.7	5.7	2.0	2.0
8 Filter	5.5	1.7		5.7	2.0	

Table 3.5.10 Size distribution data for Fig. 3.33

Sample	counts	% -T	cumulative % undersize	µg salbutamol	% -T	cumulative % undersize
Can 4a	x10-2					
Throat (T)	1733.9			319.8		
0	9.1	1.1	98.9	3.3	1.6	98.5
1	21.4	2.7	96.2	6.3	3.0	95.5
2	58.5	7.4	88.8	14.6	6.9	88.6
3	232.7	29.6	59.2	55.0	25.9	62.7
4	217.8	27.7	31.5	59.4	27.9	34.8
5	182.4	23.2	8.3	52.2	24.6	10.2
6	38.4	4.9	3.4	9.8	4.6	5.6
7	11.6	1.5	1.9	4.7	2.2	3.4
8 Filter	14.7	1.9		7.3	3.4	
Can 4b						
Throat (T)	93.4			202.0		
0	7.9	2.4	97.6	2.4	1.8	98.0
1	11.4	3.4	94.2	3.7	2.8	95.2
2	20.3	6.1	88.1	6.1	4.6	90.6
3	60.7	18.2	69.9	28.5	21.6	69.0
4	51.0	15.3	54.6	34.1	25.9	43.1
5	124.5	37.2	17.4	38.6	29.3	13.8
6	32.0	9.6	7.8	8.6	6.5	7.3
7	12.5	3.7	4.1	4.8	3.6	3.7
8 Filter	14.0	4.1		4.9	3.7	
Can 1 (c&d)						
Throat (T)				677.4		
0				3.6	1.5	98.5
1				2.7	1.2	97.3
2				4.4	1.9	95.4
3				28.4	12.2	83.2
4				101.6	43.5	39.7
5				74.6	31.9	7.8
6				10.2	4.4	3.4
7				1.8	0.7	2.7
8 Filter				6.4	2.7	

Table 3.5.11 Size distribution data for Fig. 3.34

Sample	counts	%	%-T	cumulative % undersize
Can 1				
Throat (T)	95800	62.3		
0	780		1.3	98.5
1	1810		3.1	95.4
2	1450		2.5	92.9
3	3450		5.9	87.0
4	5070		8.7	78.3
5	17970		31.0	47.3
6	16140		27.8	19.5
7	8620		14.9	4.6
8 Filter	2663		4.6	
Can 2				
Throat (T)	65450	68.6		
0	660		2.2	97.7
1	790		2.6	95.1
2	840		2.8	92.3
3	1410		4.7	87.6
4	2360		7.9	79.7
5	7740		25.8	53.9
6	8880		29.7	24.2
7	5180		17.3	6.9
8 Filter	2075		6.9	

APPENDIX 4 - IN VIVO STUDIES

Appendix 4.1 Size distribution data of metered-dose inhalers containing Tc-Ph_4AsCl used for imaging (measured by Andersen Sampler).

Experiment Code		Salbutamol		Technetium-99m	
		Mean Diameter d_{gw} (μm)	σg	Mean Diameter d_{act} (μm)	σg
Group 1 (n = 7)	(250103	3.4	2.2	3.6	2.5
	(020283	2.85	1.5	2.95	1.5
	(080283	2.6	1.5	2.7	1.6
	(090283	3.1	1.9	3.65	1.6
	(140283	3.2	1.6	3.15	1.6
	(210283	2.9	1.5	3.25	1.5
	(230283	2.95	1.5	3.15	1.6
geometric mean	(S.D.)	3.0 (1.1)	1.7 (1.2)	3.2 (1.1)	1.7 (1.2)
Group 2 (n = 3)	(150183	3.4	2.8	3.8	2.4
	(010383	3.6	2.3	4.85	2.1
	(160383	3.9	2.5	4.8	1.7
geometric mean	(S.D.)	3.6 (1.1)	2.5 (1.1)	4.5 (1.1)	2.0 (1.2)
Group 3 (n = 5)	(010201	4.3	3.2	9.0	3.5
	(010203	3.65	2.4	6.1	2.0
	(070283	3.9	2.6	6.9	2.0
	(150283	3.3	3.1	7.7	3.2
	(220283	3.4	1.9	5.5	2.9
geometric mean	(S.D.)	3.7 (1.1)	2.6 (1.2)	6.9 (1.2)	2.6 (1.3)
Group 4 (n = 7)	(140183	4.2	3.9	7.5	2.0
	(260183	3.4	6.9	8.7	2.8
	(070383	6.4	1.6	4.0	1.9
	(080383	5.0	3.1	4.0	1.8
	(090383	6.5	4.4	5.8	3.1
	(140383	5.6	2.3	2.6	1.8
	(280383	4.7	2.2	3.9	2.2
geometric mean	(S.D.)	5.0 (1.3)	3.1 (1.6)	4.8 (1.5)	2.2 (1.2)

Appendix 4.2 Dose delivery of salbutamol in metered-dose inhalers containing Tc-Ph_4AsCl.

Experiment	Code	Initial Activity Used in Prepn. (mCi)	Count (k) in 2 shots by Camera	Q.C. in Andersen Sampler			
				No. of shots	Total Counts (k)	Total ug Salbutamol	Dose/Shot (UG)
	250103	14.9	94	40	2310	1180	29.5
	020283	13.5	50	40	5329	964	24.1
Group 1	080283	19.7	20	40	3911	945	23.6
	090283	11.0	49	40	22931	984	24.6
n = 7	140283	13.3	65	40	4222	1006	25.2
	210283	15.6	85	40	3688	819	20.5
	230283	23.6	76	40	2112	1051	26.3
geometric mean (S.D.)							24.6 (1.1)
Group 2	150183	18.4	42	40	2058	707	17.7
	010383	12.8	67	40	678	526	13.2
n = 3	160383	19.2	214	30	664	627	20.9
geometric mean (S.D.)							17.0 (1.3)
	010201	11.7	76	35	1941	474	13.5
Group 3	010203	16.9	91	40	2056	870	21.8
	070283	22.4	74	40	2014	782	19.6
n = 5	150283	20.3	112	40	1704	492	12.3
	220283	17.2	59	40	7840	489	12.2
geometric mean (S.D.)							15.4 (1.3)
	140183	14.9		40	13118	606	15.2
	260183	14.0	68	40	1167	792	19.8
Group 4	070383	33.3	103	40	1338	708	17.7
	080383	20.9	94	40	1834	636	15.9
n = 7	090383	16.4	49	40	1392	381	9.5
	140383	16.1	103	40	7908	813	20.3
	280383		81	40	2378	598	15.0
geometric mean (S.D.)							15.8 (1.3)

Appendix 4.3 Variability in breathing pattern of beagle dogs during dosing with a placebo metered dose inhaler

Experiment Code	Dog 1				Dog 2			
	Tidal volume (ml)	Breathing rate (min-1)	Inspiratory flow rate (l min-1)	minute volume (ml)	Tidal volume (ml)	Breathing rate (min-1)	Inspiratory flow rate (l min-1)	minute volume (ml)
1. 140483	253	16	7.8	4289	219	22	10.5	4995
2. 140483A	233	22	11.3	5349	312	16	10.1	5296
3. 150483	227	19	9.0	4503	204	21	9.3	4479
4. 150483A	226	46	18.9	10514	277	32	14.8	9070
5. 180483	170	29	8.7	4981	289	21	11.0	6346
6. 180483A	336	30	19.3	10323	453	20	17.9	9461
7. 190483	253	50	28.6	12770	391	16	10.8	6471
8. 190483A	334	28	13.4	9451	422	19	15.0	8412
9. 200483	242	21	9.0	5210	363	18	11.9	6581
10. 200483A	207	30	12.0	6260	398	23	15.5	9439
Median	238	29	11.7	5805	338	21	11.5	6526
Range	(170-336)	(16-50)	(7.8-28.6)	(4289-12770)	(204-453)	(16-32)	(9.3-17.9)	(4479-9461

Appendix 4.4 Variability in breathing pattern of beagle dogs during dosing with MDI's containing Salbutamol (Groups 1 - 4)

Experiment Code	Dog 1				Dog 2			
	Tidal volume (ml)	Breathing rate (min-1)	Inspiratory flow rate (l min-1)	minute volume (ml)	Tidal volume (ml)	Breathing rate (min-1)	Inspiratory flow rate (l min-1)	minute volume (ml)
Group 1								
250103				no data				
020283	293	15	9.8	4420	225	19	12.5	4371
080283	191	22	8.7	4260	281	16	11.1	4774
090283	291	18	9.8	5439	236	22	9.6	5407
140283	217	21	10.2	4707	257	15	8.0	4036
210283	180	20	6.6	3742	337	16	12.8	5427
230283	279	22	13.5	6154	363	15	10.9	5601
Median	248	20.5	9.8	4564	269	16	11.0	5091
Range	(180-293)	(15-22)	(6.6-13.5)	(3742-6154	(225-363)	(15-22)	(8.0-12.8)	(4036-5601)
Group 2								
150183	252	15	11.8	3829	223	17	17.4	3812
010383	257	31	15.4	8212	422	17	12.8	7520
160383	223	23	9.1	5328	276	24	12.9	6621
Median	252	23	11.8	5328	276	17	12.9	6621
Range	(223-257)	(15-31)	(9.1-15.4)	(3829-8212)	(223-422)	(17-24)	(12.8-17.4)	(3812-7520)
Group 3								
010201	260	14	8.0	3835	274	14	8.2	4095
010203	381	13	9.2	5256	303	17	12.0	5237
070283	200	38	16.8	7803	352	16	12.8	5989
150283	342	18	11.5	6472	358	14	11.7	5335
220283	215	18	7.9	3979	192	20	9.7	3961
Median	260	18	9.2	5256	303	16	11.7	5237
Range	(200-381)	(13-38)	(7.9-16.8)	(3835-7803)	(192-358)	(14-20)	(8.2-12.8)	(3961-5989)
Group 4								
140183	231	17	7.8	4016	176	16	7.9	2825
260183	177	25	9.4	4481				
070383	75	37	5.7	2799	180	30	21.8	5533
080383	232	36	16.7	8536	271	18	10.3	5077
090383	272	15	9.6	4307	203	23	11.0	4776
140383	159	24	12.6	3934	324	19	37.1	6338
280383	265	11	7.5	3135	277	21	13.7	5827
Median	231	24	9.4	4016	237	20	12.4	5305
Range	(75-272)	(11-37)	(5.7-16.7)	(2799-8536)	(176-324)	(16-30)	(7.9-37.1)	(2825-63338)

Appendix 4.5 Summary of HSA deposition data including administration devices

RABBIT B	Counts In Tube	% In Tube	Counts In Chbr.	% In Chbr.	Total Admin. Counts	Total Admin. %	% Lungs	% Stomach	% Head	Total Body Counts
250882					50555	84.0	4.0	7.5	4.5	9594
030982					7535	85.9	2.8	6.2	5.1	1235
DOG 1										
190882	20794	58.1	1732	4.8	22526	62.9	19.7	4.5	12.9	13293
200801	21366	63.7	5087	15.2	26453	78.9	16.4	1.9	2.0	6805
230801	23408	62.9	4483	12.0	27891	74.9	16.4	4.5	4.2	9353
020902	8949	51.2	1940	11.1	10889	62.3	26.7	3.9	7.1	6591
030901	18111	51.5	2746	7.8	20857	59.3	22.8	7.4	10.5	14296
051082 (n=6)	46390	68.4	6144	9.1	52534	77.5	13.1	3.4	6.0	15270
Median Range		60.5 (51.2-68.4)		10.1 (4.8-15.2)		68.9 (59.3-78.9)	18.1 (13.1-26.7)	4.2 (1.9-7.4)	6.6 (2.0-12.9)	
DOG 2										
200801	20515	51.0	3975	9.9	24490	60.9	12.9	6.8	19.4	15738
230802	14092	55.2	1830	7.2	15922	62.4	20.0	5.4	12.3	9620
020901	20683	46.5	4523	10.2	25206	56.7	19.2	15.4	8.7	19257
030902	12928	44.0	3488	11.9	16416	55.9	27.5	6.6	10.1	12953
051001 (n=5)	16931	66.6	1489	5.9	18420	72.5	14.9	5.5	7.2	6994
Median Range		51.0 (44.0-66.6)		9.9 (5.9-11.9)		60.9 (55.9-72.5)	19.2 (12.9-27.5)	6.6 (5.4-15.4)	10.1 (7.2-19.4)	

Appendix 4.6
Table 4.6.1 Deposition of metered dose aerosols containing TcPh4AsCl (Group 1) including administration devices.

Dog 1

Experiment Code	Counts in Chamber	Total Body Counts	% Chamber	% Total Body	% Lungs	% Stomach	% Head % URT
250103	37968	5647	87.0	12.9	9.5	1.9	1.5
020283	9546	6192	60.7	39.3	31.3	3.4	4.6
080283	3550	1826	66.0	34.0	27.5	3.0	3.4
090283	12517	4450	73.8	26.2	14.2	4.8	7.2
140283	14787	6604	69.1	30.9	23.6	2.0	5.2
210283	23120	7816	74.7	25.3	19.9	1.5	3.8
230283	17620	7909	69.0	31.0	23.0	2.2	5.7
Median			69.1	30.9	23.0	2.2	4.6
Range			(60.7-87.0)	(12.9-39.3)	(9.5-31.3)	(1.5-4.8)	(1.5-7.2)

Dog 2

250103	26316	2231	92.2	7.8	1.3	1.4	5.1
020283	11209	3536	76.0	24.0	16.5	3.6	3.8
080283	5446	1447	79.0	21.0	9.5	3.7	7.8
090283	13781	4574	75.1	24.9	16.1	2.9	5.9
140283	9943	6152	61.8	38.2	4.3	7.2	26.7
210283	18231	10682	63.1	36.9	2.9	5.4	28.7
230283	18622	7305	71.8	28.2	4.3	8.8	15.1
Median			75.1	24.9	4.3	3.7	7.8
Range			(61.8-92.2)	(7.8-38.2)	(1.3-16.5)	(1.4-8.8)	(3.8-28.7)

Appendix 4.6

Table 4.6.2 Deposition of metered dose aerosols containing TcPh4AsCl (Group 2 & 3) including administration devices.

Dog 1

Experiment Code	Counts in Chamber	Total Body Counts	% Chamber	% Total Body	% Lungs	% Stomach	% Head % URT
150183	11635	3012	79.4	20.6	15.4	2.7	2.5
010383	15189	2956	83.7	16.3	9.5	2.9	3.9
160383	60012	12328	83.0	17.0	10.2	3.8	3.0
Median Range			83.0 (79.4-83.7)	17.0 (16.3-20.6)	10.2 (9.5-15.4)	2.9 (2.7-3.8)	3.0 (2.5-3.9)
010201	20723	1575	92.9	7.1	3.0	0.7	3.4
010203	22498	4909	82.1	17.9	11.9	3.0	3.0
070283	13123	2125	86.1	13.9	7.0	2.7	1.8
150283	24782	2523	90.8	9.2	4.7	1.9	2.6
220283	13725	1857	88.1	11.9	8.5	1.5	1.9
Median Range			88.1 (82.1-92.9)	11.9 (7.1-17.9)	7.0 (3.0-11.9)	1.9 (0.7-3.0)	2.6 (1.8-3.4)
Dog 2							
150183	10762	3769	74.1	25.9	4.1	16.4	5.5
010383	17378	1887	90.2	9.8	1.6	2.1	6.0
160383	56323	7308	88.5	11.5	2.5	4.8	4.1
Median Range			88.5 (74.1-90.2)	11.5 (9.8-25.9)	2.5 (1.6-4.1)	4.8 (2.1-16.4)	5.5 (4.1-6.0)
010201	16996	1322	92.8	7.2	0.5	3.9	2.7
010203	34069	2502	93.2	6.8	2.2	2.3	2.3
070283	15677	841	94.9	5.1	1.7	0.2	3.2
150283	18084	2759	86.8	13.2	1.7	2.8	8.8
220283	17343	2683	86.6	13.4	4.0	6.5	2.9
Median Range			92.8 (86.6-94.9)	7.2 (5.1-13.4)	1.7 (0.5-4.0)	2.8 (0.2-6.5)	2.9 (2.3-8.8)

Appendix 4.6
Table 4.6.3 Deposition of metered dose aerosols containing TcPh4AsCl (Group 4) including administration devices.

Dog 1

Experiment Code	Counts in Chamber	Total Body Counts	% Chamber	% Total Body	% Lungs	% Stomach	% Head % URT
140183	21194	1774	92.3	7.7	2.1	4.6	1.0
260183	25986	1140	95.8	4.2	2.3	0.9	1.0
070383	27531	6964	79.8	20.2	15.4	1.3	3.5
080383	24507	6820	78.2	21.8	14.6	1.6	5.6
090383	18314	1938	90.4	9.6	5.4	1.4	2.8
140383	39675	9246	81.1	18.9	7.5	7.5	3.9
280383	22178	7940	73.6	26.4	7.7	15.1	3.6
Median			81.1	18.9	7.5	1.6	3.5
Range			(73.6-95.8)	(4.2-26.4)	(2.1-15.4)	(0.9-15.1)	(1.0-5.6)

Dog 2

140183	20837	1906	91.6	8.4	1.5	3.1	3.8
260183	12898	792	94.2	5.8	1.3	2.0	2.4
070383	59340	7033	89.4	10.6	1.1	2.1	7.4
080383	26446	7024	79.0	21.0	4.4	10.3	6.3
090383	17815	2180	89.1	10.9	1.8	2.0	7.1
140383	40644	8039	83.5	16.5	1.1	2.2	13.2
280383	22784	6387	78.1	21.9	16.6	1.6	3.6
Median			89.1	10.9	1.5	2.1	6.3
Range			(78.1-94.2)	(5.8-21.9)	(1.1-16.6)	(1.6-10.3)	(3.6-13.2)

Appendix 4.7 Deposition of HSA aerosols in rabbits

RABBIT A

Experiment code	Time after dosing (mins)	Body Distribution						Remarks
		Lungs		Stomach		Head & URT		
		corrected counts	%	corrected counts	%	correct counts	%	
060582 P321/39	2	558	14.4	2965	76.8	339	8.8	6-7 mins Admin.
160302 P321/40	2	2823	12.0	11556	49.3	9059	38.6	via Drying 10L chamber
230882 P321/48	2	2548	10.5	11485	47.3	10243	42.2	10 mins Admin.
020982 P321/53	2	2092	14.5	9073	61.1	3686	24.8	
030982 P321/56	2	115	12.1	649	68.2	188	19.7	Via Drying 10L chamber
Median Range			12.1 (10.5-14.5)		61.1 (47.3-76.8)		24.8 (8.8-42.2)	
RABBIT B								
060582 P321/39	2	1566	22.9	4464	65.4	797	11.7	10 mins Admin.
160302 P321/40	2	7499	35.0	11015	51.4	2918	13.6	via Drying 10L chamber
230882 P321/48	2	3238	30.8	4053	38.6	3204	30.5	10 mins Admin.
250882 P321/51	2	2379	24.8	4528	47.2	2687	28.0	Via wide glass tubing + thermotrace
020982 P321/53	2	2482	31.2	2929	36.8	2543	32.0	
030982 P321/56	2	247	20.0	540	43.7	448	36.3	Via Drying 10L chamber
Median Range			27.8 (20.0-35.0)		45.5 (36.8-65.4)		29.3 (11.7-36.3)	

URT = Upper respiratory tract

Appendix 4.8 Deposition of HSA aerosols in dogs

DOG 1

Experiment code	Time after dosing (mins)	Body Distribution					
		Lungs		Stomach		Head & URT	
		corrected counts	%	corrected counts	%	corrected counts	%
190882	2	7060	53.1	1625	12.2	4604	34.6
200801	3	5486	80.6	647	9.5	672	9.9
230801	3	6109	65.3	1691	18.1	1553	16.6
240802	3	4769	72.5	563	8.6	1240	18.9
020902	3	4668	70.8	688	10.4	1235	18.7
030901	3	8011	56.0	2588	18.1	3697	25.9
051082	3	8904	58.0	2323	15.0	4043	26.0
Median Range			65.3 (53.1-80.6)		12.2 (8.6-18.1)		18.9 (9.9-34.6)
DOG 2							
200801	3	5189	33.0	2727	17.3	7822	49.7
230802	3	5105	53.1	1370	14.2	3145	32.7
240801	4	8119	51.9	2583	16.5	4935	31.5
020901	3	8536	44.3	6836	35.5	3885	20.2
030902	3	8062	62.2	1933	14.9	2958	22.8
051001	2	3774	54.0	1389	20.0	1831	26.0
Median Range			52.5 (33.0-62.2)		16.9 (14.2-35.5)		28.8 (20.2-49.7)

Appendix 4.9

Table 4.9.1 Deposition of HSA aerosols in lung periphery in rabbits and dogs.

Animal	Experiment Code	Time After Dosing (Mins)	Corrected Counts			% Peripheral
			Total Lungs	Central Airways	Peripheral Airways	Total
Rabbit B	160302	2	6737	4257	2480	36.8
	230882	2	2786	1850	936	33.6
	250882	2	2011	1527	484	24.1
	020982	2	2257	1836	421	18.7
	Median and range					28.9 (18.7-36.8)
Dog 1	190882	2	6840	5634	1206	17.6
	200801	3	5421	4492	929	17.1
	230801	3	5740	4329	1411	24.6
	240802	3	4139	3287	852	20.6
	020902	3	4710	4168	542	11.5
	030901	3	7694	6166	1528	19.9
	051082	4	8881	6132	2749	31.0
	Median and range					19.9 (11.5-31.0)
Dog 2	190882	2	3925	3242	683	17.4
	200801	3	4915	4380	535	10.9
	230802	3	4892	3852	1040	21.3
	240801	4	7240	5027	2213	30.6
	020901	3	8429	6464	1965	23.3
	030902	3	7574	6145	1429	18.9
	051001	2	3443	2825	618	17.9
	Median and range					18.9 (10.9-30.6)

Appendix 4.9

Table 4.9.2 Deposition of Tc-Ph4AsCl aerosols in lung periphery in Dog 1.

Experiment Code	Time After Dosing (Mins)	Corrected Counts			% Peripheral
		Total Lungs	Central Airways	Peripheral Airways	Total
250103)	3	4202	3560	642	15.3
020283)	3	4019	3431	588	14.6
080283)(Group 1)	3	1475	1190	285	19.3
090283)	3	2447	1887	560	22.9
140283) n = 7	3	4638	4039	599	12.9
210283)	3	6110	5445	665	10.9
230283)	3	5797	5093	704	12.1
Median and range					14.6 (10.9-22.9)
150183)(Group 2)	3	1827	1455	372	20.4
010383)	3	1591	1364	227	14.3
160383) n = 3	3	6170	5608	562	9.1
Median and range					14.3 (9.1-20.4)
010203)(Group 3)	3	3433	2864	569	16.6
070283)	3	931	812	119	12.8
150283) n = 3	2	1403	1030	373	26.6
Median and range					16.6 (12.8-26.6)
070383)(Group 4)	3	4949	4296	653	13.2
080383)	3	4072	3426	646	15.9
140383) n = 3	6	3520	2874	883	25.1
Median and range					15.9 (13.2-25.1)

Appendix 4.10 Deposition of nebulised salbutamol aerosols in dogs.

DOG 1

Experiment Code	Time After Dosing (mins)	Body Distribution							
		Total Lungs		Stomach		Head & URT		Periph. Lungs (of Total lungs)	
		corrected counts	%	corrected counts	%	corrected counts	%	corrected counts	%
210383	3	7701	42.9	2532	14.1	7712	43.0	1319/6283	21.0
220383	3	2178	63.2	255	7.4	1012	29.4	-	
DOG 2									
210383	2	9287	79.1	1180	10.0	1272	10.8	1672/8536	19.6
220383	2	10737	53.5	1281	6.4	8065	40.1	2080/10010	20.8
Median (range)		58.4 (42.9-79.1)		8.9 (6.4-14.1)		34.8 (10.8-43.0)		20.8 (19.6-21.0)	

Note Parameters of Activity and Mass size distributions for this type of aerosol are:
Salbutamol: mean diameter 1.50µm g 1.60
Technetium-99m: mean diameter 1.42µm g 1.65

Appendix 4.11 Clearance of HSA aerosol in Rabbit B

Study No. 160302

Time After Dosing (mins)	Body Distribution						Total Corrected counts
	Lungs		Stomach		Head & URT		
	Corrected counts	%	Corrected counts	%	Corrected counts	%	
2	7499	35.0	11015	51.4	2918	13.6	21432
6	5769	24.6	14210	60.6	3470	14.8	23449
10	5676	24.6	14256	61.8	3133	13.6	23065
19	5416	24.1	15153	67.3	1940	8.6	22509
23	5296	22.9	15550	67.4	2228	9.6	23074
32	5199	22.4	16877	72.7	1149	4.9	23225
42	5118	21.4	17955	75.0	857	3.6	23930

Appendix 4.12 Clearance of HSA aerosol in Dog 1

Study No. 230801

Time After Dosing (mins)	Body Distribution						Total Corrected counts
	Lungs		Stomach		Head & URT		
	Corrected counts	%	Corrected counts	%	Corrected counts	%	
3	6109	65.3	1691	18.1	1553	16.6	9353
7	6789	67.3	2241	22.2	1113	10.5	10089
13	6727	68.8	2010	20.6	1004	10.6	9770
17	6958	68.8	1969	19.5	1180	11.7	10107
20	7831	70.9	2039	18.5	1062	10.6	10932
75	6519	76.8	1248	14.7	724	8.5	8491

Appendix 4.13 Deposition of metered-dose aerosols containing Tc-Ph_4AsCl (Group 1)

Table 4.13.1

DOG 1

Experiment code	Time After Dosing (min)	Body Distribution					
		Lungs		Stomach		Head & URT	
		Corrected counts	%	Corrected counts	%	Corrected counts	%
250103	3	4128	73.1	846	15.0	673	11.9
020283	3	4929	79.6	537	8.7	726	11.7
080283	3	1480	81.0	161	8.8	185	10.1
090283	3	2408	54.1	812	18.2	1230	27.6
140283	3	5049	76.4	435	6.6	1120	16.9
210283	3	6161	78.8	466	6.0	1189	15.2
230283	3	5881	74.3	569	7.2	1459	18.4
Median (range)		76.4 (54.1-81.0)		8.7 (6.0-18.2)		15.2 (10.1-27.6)	
DOG 2							
250103	3	364	16.3	413	18.5	1454	65.2
020283	3	2439	69.0	531	15.0	566	16.0
080283	3	658	45.5	252	17.4	537	37.1
090283	3	2960	64.7	525	11.5	1089	23.8
140283	3	687	11.2	1164	18.9	4301	69.9
210283	3	835	7.8	1555	14.5	8292	77.6
230283	3	1115	15.3	2278	31.2	3912	53.5
Median (range)		16.3 (7.8-69.0)		17.4 (11.5-31.2)		53.5 (16.0-77.6)	

Table 4.13.2 Deposition of metered-dose aerosols containing Tc-Ph_4AsCl (Groups 2 & 3)

DOG 1

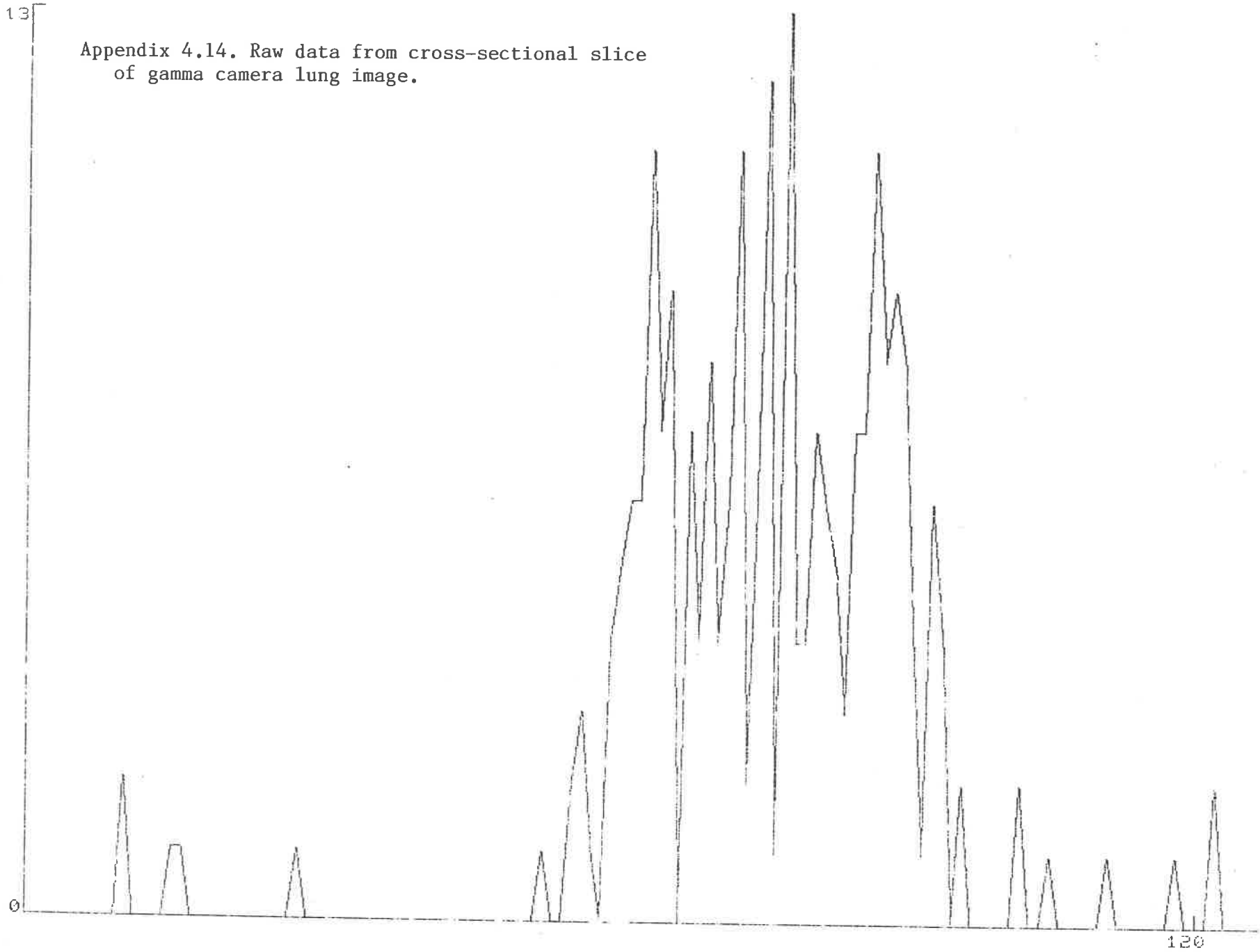
Experiment code	Time After Dosing (min)	Body Distribution					
		Lungs		Stomach		Head & URT	
		Corrected counts	%	Corrected counts	%	Corrected counts	%
150183	3	2257	74.9	393	13.0	362	12.1
010383	3	1728	58.5	525	17.8	703	23.8
160383	3	7386	59.9	2733	22.2	2209	17.9
Median (range)		59.9 (58.5-74.9)		17.8 (13.0-22.2)		17.9 (12.1-23.8)	
010201	3	659	41.8	157	10.0	759	48.2
010203	3	3257	66.3	823	16.8	829	16.9
070283	3	1066	50.2	410	19.3	649	30.5
150283	2	1287	51.0	529	21.0	707	28.0
220283	3	1322	71.2	236	12.7	299	16.1
Median (range)		51.0 (41.8-71.2)		16.8 (10.0-21.0)		28.0 (16.1-48.2)	
DOG 2							
150183	3	591	15.7	2381	63.2	797	21.1
010383	3	309	16.4	420	22.2	1158	61.4
160383	3	1609	22.0	3083	42.2	2616	35.8
Median (range)		16.4 (15.7-22.0)		42.2 (22.2-63.2)		35.8 (21.1-61.4)	
010201	3	95	7.2	724	54.8	503	38.0
010203	3	806	32.2	856	34.2	840	33.6
070283	3	279	33.2	41	4.9	521	61.9
150283	3	347	12.6	580	21.0	1832	66.4
220283	3	807	30.1	1302	48.5	574	21.4
Median (range)		30.1 (7.2-33.2)		34.2 (4.9-54.8)		38.0 (21.4-66.4)	

Table 4.13.3 Deposition of metered-dose aerosols containing Tc-Ph_4AsCl (Group 4)

DOG 1

Experiment code	Time After Dosing (min)	Body Distribution					
		Lungs		Stomach		Head & URT	
		Corrected counts	%	Corrected counts	%	Corrected counts	%
140183	3	488	27.5	1059	59.7	227	12.8
260183	3	634	55.6	246	21.6	260	22.8
070383	3	5317	76.3	445	6.4	1202	17.3
080383	3	4573	67.0	505	7.4	1742	25.5
090383	3	1087	56.1	280	14.4	571	29.5
140383	6	3672	39.7	3668	39.7	1906	20.6
280383	3	2326	29.3	4537	57.1	1077	13.6
Median (range)		55.6 (27.5-76.3)		21.6 (6.4-59.7)		20.6 (12.8-29.5)	
DOG 2							
140183	3	349	18.3	700	36.7	857	45.0
260183	3	183	23.1	275	34.7	334	42.2
070383	3	724	10.3	1368	19.5	4941	70.2
080383	4	1480	21.1	3431	48.8	2113	30.1
090383	3	362	16.6	398	18.2	1420	65.1
140383	4	555	6.9	1052	13.1	6432	80.0
280383	2	4854	76.0	476	7.5	1057	16.5
Median (range)		18.3 (6.9-76.0)		19.5 (7.5-48.8)		45.0 (16.5-80.0)	

Appendix 4.14. Raw data from cross-sectional slice of gamma camera lung image.



APPENDIX 5 - PUBLICATIONS

1. Malton, C.A., Hallworth, G.W., Padfield, J.M., Perkins A., Wilson, C. and Davis S.S. (1982) J. Pharm. Pharmacol. 64P 'Deposition and Clearance of Inhalation Aerosols in Dogs and Rabbits using a gamma camera'.

2. Malton, C.A., Hallworth, G.W. and Padfield, J.M. (1982) J. Pharm. Pharmacol. 65P. 'The Association and Particle Size Distribution of Drug and Surfactant Discharged from a metered-dose inhalation aerosol'.

3. Malton, C.A., Wilson, C.G., Perkins, A. and Hallworth, G.W. (1983) J. Pharm. Pharmacol. 35 Suppl. 9P. 'Deposition of Pharmaceutical Aerosols in the Dog'.

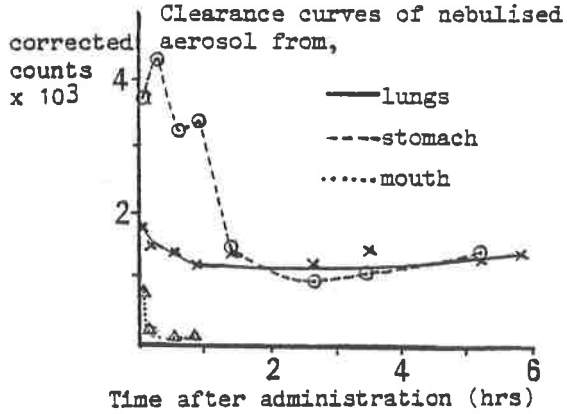
Deposition and clearance of inhalation aerosols in dogs and rabbits using a gamma camera.

C.A. Malton*, G.W. Hallworth*, J.M. Padfield*, A. Perkins**, C. Wilson** & S.S. Davis**, Glaxo Group Research Ltd., Ware* and University of Nottingham**, UK.

Administration of metered-dose aerosols to animals is complicated by the need to actuate the aerosol at the beginning of inspiration to obtain optimum lung deposition (Newman et al, 1980) and by the pharmacological effects of anaesthetics used for intratracheal administration (Patrick & Sterling, 1977) needed to by-pass the filtering effect of the nasal passages.
Administration devices previously described in the literature (Poynter & Spurling, 1971; Halpern & Schlesinger, 1980) have been modified to administer nebulised and metered-dose aerosols to conscious rabbits and beagle dogs. After dosing with ^{99m}Tc-labelled preparations, the animals were imaged using a gamma camera for the assessment of initial aerosol deposition patterns and clearance rates. Aerosols for administration were generated either from a shielded De-Vilbiss type nebuliser, or from metered-dose inhalers.
Eight experiments were conducted using trained rabbits and dogs by administering a nebulised solution of salbutamol and sodium pertechnetate in aqueous ethanol. The differences in initial aerosol deposition are shown in the table below:

	% of total body dose deposited		
	lungs	stomach	mouth
rabbits (n=4)	15±12	52± 8	25±15
dogs (n=4)	55± 9	25±14	8± 3

The mass median diameter of the droplets was 6.5±0.5µm.
The increased lung deposition in dogs may be explained by:
(i) the administration device acts as a drying chamber, thereby reducing the mean aerosol droplet size.
(ii) the delivery tubing is wider, thus reducing wall losses, and the end of the tube is shaped to seal the trachea, so reducing the amount of aerosol deposited in the mouth or swallowed.
The Figure shows a typical result from an experiment conducted in a rabbit. The relative quantities and rates of clearance vary with species and with aerosol formulation. The graph shows that the activity cleared from the lungs and mouth within the first hour goes into the stomach, from which it is subsequently cleared.



The initial deposition patterns are influenced by differences in breathing rate and tidal volume for example, so that careful monitoring is required.

Halpern,M. & Schlesinger,R.B.(1980)J.Toxicol. & Environ.Hlth.6 751-755.
Newman,S.P.et al(1980)J.Royal Soc.Med. 73(11)776-779.
Patrick,G. & Sterling,C.(1977)J.Appl.Physiol. 42(3)451-455.
Poynter,D. & Spurling,N.W.(1971)Postgrad.Med.H.Supp.47 21-25.

THE ASSOCIATION AND PARTICLE SIZE DISTRIBUTION OF DRUG AND SURFACTANT DISCHARGED FROM A METERED-DOSE INHALATION AEROSOL.

C.A. Malton, G.W. Hallworth & J.M. Padfield, Glaxo Group Research Ltd., Ware, UK.

Hygroscopic drug particles may increase in size when inhaled (Gonda, 1981), although there is recent evidence that surfactants present in inhalation aerosols may inhibit such growth (Martonen, 1980). Since particle size is a major factor governing drug deposition in the lung, the association between drug and surfactant is crucial to the role of the latter in the discharged aerosol. Ventolin Inhaler is a suspension aerosol containing salbutamol with oleic acid (10% w/w of drug) as surfactant. Forty metered doses of Ventolin Inhaler were discharged into an eight-stage Andersen sampler (Andersen, 1966), which measures the aerodynamic size distribution of aerosols by cascade impaction. Samples from each impactor stage were analysed for salbutamol and oleic acid by colorimetry and gas chromatography respectively. The results are presented as log-probability graphs of particle size (AD = aerodynamic diameter in µm) vs. cumulative weight % undersize. (Fig. 1).

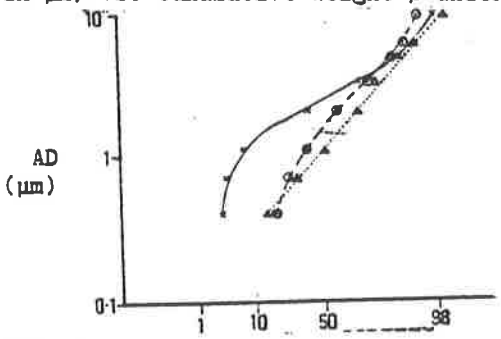


Fig. 1

Salbutamol (Ventolin Inhaler) MMAD 2.4µm g 1.5
Oleic acid (Ventolin Inhaler) MMAD 1.5µm g 2.1
Oleic acid (placebo inhaler) MMAD 1.1µm g 2.5
g -geometric standard deviation

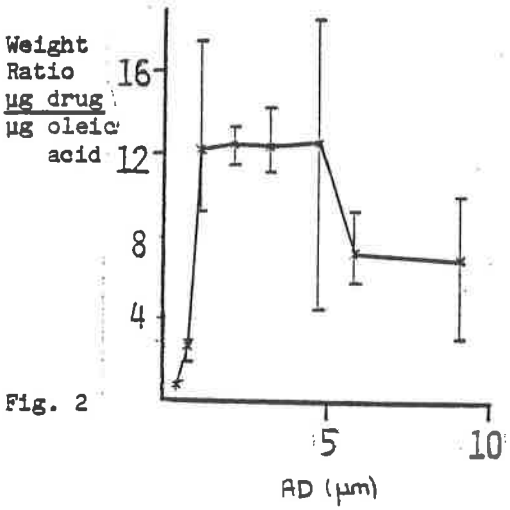


Fig. 2

Figure 1 shows that the particle size distribution of oleic acid in a placebo inhaler is log-normal and this distribution is changed by the presence of salbutamol particles in Ventolin Inhaler. The largest differences between the salbutamol and oleic acid distributions occur below 1µm; see also Figure 2. Assuming distribution of propellant droplets in the discharged spray to be log-normal, and a uniform suspension entering the atomizing nozzle of the inhaler, the size separation of the two components in the discharged aerosol may be explained by two factors:

(i) The oleic acid is in solution in the propellant mixture.

(ii) Calculations from the oleic acid distribution of the initially discharged spray droplet size distribution show that there are far more discharged droplets than drug particles; this ratio increases steeply below 1µm. It follows that the decreasing tendency for droplets to contain drug particles is enhanced as the droplet size decreases.

Above 1µm the weight ratio of drug to oleic acid corresponds to the theoretical composition of the inhaler contents.

Andersen,A.A.(1966)Am.Ind.Hyg.Assoc.J. 27 160-165.
Gonda,I.(1981) Particle Size Analysis Conference Proceedings, Loughborough.
Martonen,T.B.(1980). Proceedings 5th Int. Symp. on Inhaled Particles, Cardiff.

DEPOSITION OF PHARMACEUTICAL AEROSOLS IN THE DOG

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The use of a suitable animal model for studying biopharmaceutical aspects of inhalation aerosols can be particularly valuable in the research and development of new formulations. In vivo/in vitro correlations of aerosol behaviour may indicate the optimum particle size and dosage form, and the use of animal models produces this information in the early stages of formulation development.

A method has been developed which correlates the in vivo aerosol deposition pattern in conscious beagle dogs measured by a gamma camera, with the in vitro particle size distribution measured by an 8-stage cascade impactor. Aerosol formulations were labelled with technetium-99m and generated from a shielded nebuliser or a pressurised metered-dose inhaler (MDI). A rubber tube fitted to an administration chamber, (Poynter, & Spurling, 1971) delivered aerosol into the pharynx of the dog, and simultaneous spirometer measurement of breathing patterns allowed the metered-dose inhaler to be fired at the correct point in the breathing cycle.
Two beagle dogs were used, and the baseline variability in breathing pattern established using placebo MDI's containing propellants only. The biological variability in aerosol deposition pattern as measured with the gamma camera was established using a nebulised aerosol of human serum albumin millimicrospheres (0.5µm).

Aerosol	AMAD (µm)	% chamber Dog1	% chamber Dog2	% total lungs Dog1	% total lungs Dog2	% stomach/pharynx Dog1	% stomach/pharynx Dog2
MDI-1 (5)	3.0 (2.7-3.2)	68 (61-75)	70 (62-79)	25 (20-31)	7 (3-16)	7 (4-9)	22 (8-38)
MDI-2 (3)	4.4 (3.6-4.8)	80 (74-84)	85 (75-90)	11 (9-14)	7 (2-16)	9 (6-12)	8 (6-11)
MDI-3 (5)	7.0 (5.5-9.0)	88 (82-93)	91 (87-95)	7 (3-12)	2 (0.5-4)	5 (3-7)	7 (2-15)
Nebulised HSA (7)	2.2 (2.1-2.4)	32 (11-70)	26 (16-53)	43 (21-55)	40 (24-53)	24 (8-46)	34 (14-69)

Table 1. Mean % Aerosol deposition (and range) as a function of particle size in the administration chamber and regions of interest for each dog; numbers in parentheses indicate number of experiments. AMAD= Activity median aerodynamic diameter.

The disadvantages of using animal models for studying aerosol behaviour in vivo are the differences in respiratory anatomy between animal and human species (Schlesinger, & McFadden, 1981) and the lack of control over breathing pattern. The results also show the large inherent biological variability and differences between subjects.

However, the results also demonstrate the particle size differentiation in terms of % total lung dose and the important differences in body distribution between nebulised and metered-dose aerosol formulations. The advantages of studying new aerosol formulations in vivo in the early stages of the their development clearly outweigh any disadvantages.

Poynter D. & Spurling N.W. (1971) Postgrad. Med. J. Suppl. 47 21-55
Schlesinger R.B. & McFadden L.A., (1981) Anatomical Record 199 99-108