

Labconco Corporation
Performance Verification
Precise HEPA-Filtered Glove Box
Surrogate Monitoring with Naproxen Sodium
Active Pharmaceutical Ingredient (API)

Introduction

Labconco conducted performance verification testing of the Precise HEPA-Filtered Glove Box catalog number 5220200, as a means of assessing its ability to contain and control airborne concentrations of particulate powder generated during laboratory bench-scale operations, and in an attempt to characterize the range of potential occupational exposures associated with these types of operations. Performance testing was conducted at the Labconco test facility in Kansas City, Missouri on December 13, 2007. With the goal of providing a robust challenge to the containment equipment, naproxen sodium was selected as a surrogate, non-potent active pharmaceutical ingredient and utilized throughout the course of the operations. Laboratory operations consisted of distinct manipulations of small-scale weigh-outs (e.g., 1 gram quantities) from a 100-gram, wide-mouthed source container. Specifically, the challenge was comprised of three iterations of the weighing task, each of which involved repetitive (e.g., a total of 15) 1-gram weigh-outs into screw cap glass scintillation vials at a Mettler PB 303 Delta Range[®] Balance. Each of these different iterations was performed by a unique operation in an attempt to address issues of operator technique/variability.

Naproxen sodium was selected and used as a surrogate API for this verification test for numerous reasons. Perhaps most prominently, while it is relatively non-toxic and safe to handle (with an associated occupational exposure limit (OEL) of 5 mg/m³), it is readily detectable in air at a very low nanogram/cubic meter concentrations, enabling assessment of exposure on a task-oriented basis, even in those instances where said tasks are brief in duration. Samples were taken by Labconco personnel following a protocol established by SafeBridge Consultants, Inc. for previous testing of other Labconco products such as the Xpert Balance Enclosure and the Xpert Filtered Balance System. Analytical testing of the sample collection cassettes for naproxen sodium was made by SafeBridge Consultants, Inc. (data report from SafeBridge is appended to this report). The analytical method used for testing of the naproxen sodium is capable of detecting as little as 2 nanograms of the surrogate per filter cassette using high performance liquid chromatography (HPLC) coupled with fluorescence detection. Additionally, as a crystalline API, naproxen sodium is characterized by a high dustiness quotient and exhibits challenging electrostatic properties, therein providing a robust challenge to operators (e.g., handling techniques) as well as the containment/control system (e.g., HEPA-Filtered Glove Box). This combination of characteristics lends useful insight into the potential exposures and/or levels of control that are likely to be achieved with the Precise HEPA-Filtered Glove Box where potent API's are handled in a similar fashion (e.g., during similar mass-scale and/or activity – weighing/dispensing).

Description of the Labconco Precise HEPA-Filtered Glove Box

The Labconco Precise HEPA-Filtered Glove Boxes have inlet and outlet HEPA filters and provide a leak-tight physical barrier to protect the operator from hazardous airborne particulates and powders. The box has approximately 13 cubic feet of interior space in the main chamber, 33.5" w x 27.5" d maximum x 25" high. Transfer chamber interior measures approximately 11.0" nominal ID x 12.0" long. All models feature: One-piece molded, medium-density polyethylene shell with a dry powder epoxy-coated superstructure; 1/4" thick laminated safety glass viewing window with powder-coated steel frame and neoprene gasket. Window is 26.4" w x 12.5" high. Window is easily removable for loading equipment. Each box has a black, chemical-resistant phenolic core work surface sealed to the glove box floor and interior ceiling-mounted electrical duplex receptacle with 5 amp maximum (100/115 volt models) or 2 amp maximum (230 volt models) circuit-load. Also included is a built-in blower with speed control capable of airflow from 13 CFM to 100 CFM and a fluorescent lamp, 22 watts, with easy exterior replacement from the top. The glove box includes inlet and outlet HEPA filters, 99.99% efficient on 0.3 micron particulates, and test port for challenging HEPA filter integrity. A main chamber static pressure gauge is included for monitoring HEPA filter loading.

Sampling Locations

A sampling strategy to measure airborne concentrations of surrogate at the operator breathing zone and at representative locations inside Labconco's test facility during weighing/dispensing operations was developed.

Three different operators were recruited to participate in these procedures, in an attempt to estimate the likely range of exposure variability among persons of differing skill and/or experience levels. Operator (personal) exposure measurements were obtained at the collar of each of the operators (e.g., in the operator breathing zone) during respective rounds of the weighing/dispensing activity. Other areas of measurement were at the exhaust of the HEPA filter, at the bottom of the outer transfer door near the gasket, and in the room approximately 10 feet in front of the glove box, at the approximate center of the room. An additional sample was taken in the corridor outside the test area.

Specifically, locations of the sampling cassettes were:

1. Left side of operator's collar.
2. HEPA filter exhaust outlet centered on the blower plenum opening.
3. Bottom of outer transfer door 1" from gasket seal.
4. Center of the room, approximately 10-feet in front of the Precise HEPA-Filtered Glove Box.
5. Corridor outside the test facility separated by a wall and a door. Samples were taken 30 minutes before and 30 minutes after weighing operations.

Equipment and Study Procedure

Industrial hygiene sampling was carried out in accordance with the above plan. The objective was to evaluate the performance capability of the Precise HEPA-Filtered Glove Box to contain and control airborne concentrations of particulate powder generated by laboratory bench-scale manipulations of a suitable surrogate, with the goal of ascertaining the ability of these units to successfully contain active pharmaceutical ingredients commonly encountered within a laboratory setting.

Sampling involved the collection of multiple sample sets, taken during each of the identified tasks with each task lasting a minimum of 30 minutes in duration. Specifically, the small-scale weigh out procedure varied in accordance with observed operator technique, spanning 47-63 minutes. Each procedural step involved the processing of 1-gram amounts of naproxen sodium within the Precise HEPA-Filtered Glove Box. All analytical weighings were conducted using a Mettler PB 303 Delta Range[®] analytical balance. Air samples were collected on 37-mm diameter glass fiber filter (GFF), held in two-section polystyrene cassettes, and situated atop cellulose back-up support pads. Weighings in the glove box were made with the blower speed set at 5-20% as to not disturb the analytical balance during the weighings. After completion of the weighings by the three operators, the sample vials, balance and general area inside the glove box was thoroughly cleaned by each operator with 50% ethyl alcohol. The cleaning towels were then placed in a sealed plastic bag and the outer surface of the bag cleaned. After completion of the weighings the blower speed was increased to 100% for five minutes. The inner door of the transfer chamber was then opened and sample vials and the sealed bag containing the clean up materials were placed in the transfer chamber ready for removal and the inner door closed. The sampling pumps were then shut off, inner door closed, outer door opened and the vials and waste bag removed. The procedure was followed by each of the three operators.

The study was setup to accommodate two objectives: (1) optimization of capture and/or containment of powders; and (2) minimization of air turbulence and/or interference with balance operation. The study was also set up to assess the containment/control performance of the glove box enclosure relative to the likely concentrations of surrogate API generated by the prescribed task of weighing and dispensing in the glove box and the surrounding area. Three operators each weighed 15 one gram samples with three iterations of the weighing task.

Personal and area samples were collected using SKC AirCheck 52 personal sampling pumps, which were operated at a flow rate of approximately 3.0 liters per minute. Personal sampling was accomplished by placing an appropriate cassette within the breathing zone of the operator, attached at the collar. Flow rates for all sampling pumps were pre- and post-calibrated using a DC-Lite Primary Flow Meter[®]. Verification of the calibration of the electronic flow meter is performed annually and is NIST trace-able. Sample analyses were accomplished by SafeBridge Consultants, Inc. Laboratory (Mountain View, CA) utilizing a high-pressure liquid chromatography (HPLC) system equipped with a fluorescence detector and a validated analytical method. The reporting limit of naproxen sodium, via this method, is 0.002 micrograms (or 2 nanograms) per sample filter. The SafeBridge Laboratory report is appended to this report.

Results and Discussion

Throughout the three different iterations of the weighing procedure, considerable variation in operator technique was observed. However, this variation was not reflected in the obtained analytical results. All air samples collected within the personal breathing zones of the three operators, as well as those proximate to the Precise HEPA-Filtered Glove Box during the weigh-outs, showed a range of 15.1-31.6 ng/m³ of naproxen sodium in air, indicating no appreciable release of naproxen sodium from the glove box during the testing.

All iterations transpired with a 100 gram bulk source of naproxen sodium situated at the right hand side of the Precise HEPA-Filtered Glove Box and to the right of the balance and next to the inner transfer chamber door. Spillage was observed around the bulk source of naproxen sodium, the glass scintillation vials, glove box gloves and balance during all iterations. Operator #1 showed the most spillage with operator #2 the least. Personal exposure results for operators #1 and #2 shows the minimal effects of the larger amount of spillage for operator #1.

It should be noted that operator #2 wet his paper towels with the 50% alcohol solution and filled his vials over the wet towels. This technique may have contained much of his spillage. Operator #2 also cleaned any spillage on his gloves between each weighing. Spillage occurred pretty much throughout the worksurface area of the box. Not only was spillage noted on the gloves, vials and the glove box worksurface but also in the balance itself. Each operator required considerable cleanup time. Operator #3 showed the best weighing technique and required the least amount of time to weigh his 15 samples but required the most time for clean up. Operator #1 stood during weighing and operators #2 and #3 sat during weighing to account for different operator heights. At the end of each clean up, the vial and waste bag were removed through the transfer doors. Over the course of the testing procedure, personal sample airborne concentration detection limits ranged from 19.2 ng/m³ to 31.6 ng/m³ at the operator breathing zone, 19.6 ng/m³ to 24 ng/m³ at the HEPA filter, 15.1 ng/m³ to 26.3 ng/m³ at the outer transfer chamber door and 14.8 ng/m³ to 21.1 ng/m³ in the room. The naproxen sodium concentration in the corridor, which was sampled for 30 minutes prior to the start of weighing and for 30 minutes following completion, showed a low concentration of 22.5 ng/m³ with a detectable limit of less than 12.0 ng/m³. No corrections to the sample results were made for concentrations of naproxen sodium found in the room or corridor.

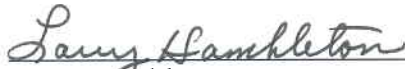
It is known that the reuse of a crystalline powder active pharmaceutical ingredient (API) can accentuate the electrostatic nature of this sort of product, thereby introducing further potential for dispersal as it is manipulated during the course of surrogate monitoring. As such, the supply of naproxen sodium was purposefully not recycled over the course of these iterations. Additionally, these procedures were characterized by temperature and humidity controlled conditions (e.g., approximately 40% relative humidity, 70° Fahrenheit).

Conclusion

In conclusion, surrogate monitoring, targeting repeated small scale weighing operations, demonstrates the effectiveness of the Precise HEPA-Filtered Glove Box in containing airborne concentrations of naproxen sodium at low nanogram/cubic meter levels. Industrial hygiene samples were taken over the course of three distinct iterations performed by different operators, with substantial variability noted in terms of work practice. All operator breathing zones, HEPA filter, transfer chamber and room samples showed no appreciable release of naproxen sodium, with detection in air for all samples below 32 ng/m^3 . These results indicate that there was no appreciable release of naproxen sodium outside of the Precise HEPA-Filtered Glove Box throughout the testing procedure, and demonstrate the potential for strategic control and containment of similar operations with other potent compounds within the same type of enclosure.

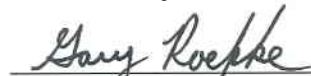
Respectfully submitted,

Prepared by:



Larry Hambleton
Chemical Safety Consultant

Reviewed by:



Gary Roepke, P.E.
Senior Product Engineer for Labconco Corporation

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Labconco Corp.
Industrial Hygiene Report
December 13, 2007

Industrial Hygiene Monitoring Data Sheet
Precise HEPA-Filtered Glove Box

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 Industrial Hygiene Report
 December 13, 2007

Location: Labconco, Kansas City, MO
 Date: December 13, 2007
 Process: Surrogate Monitoring
 One gram weighings at Precise HEPA-Filtered Glove Box

Industrial Hygiene Monitoring Data Sheet
 Building/Room: Labconco Test Facility
 Samples Collected by: Larry Hambleton, Consultant, Labconco Corp.

Sample No.	Sample Description	Job Task	Sample Media	Pump No.	Sample Period (Start)	Sample Period (Stop)	Duration (h/m)	¹ Pre-calibrated flow-rate (L/pm)	¹ Post-calibrated flow-rate (L/pm)	Sample Flow Rate (L/pm)	Sample Volume (L)	Total Naproxen Sodium (Total ng)	Airborne Concentration of Naproxen Sodium (ng/m ³)
1	Personal Sample: Breathing zone (Operator: Gary Roepke)	Dispense/Weigh 15 x 1 gm amounts of Naproxen Sodium from 100 gm container	37 mm, 1 µ GFF	1	0	58	58	2.986	2.886	2.94	170.5	5.38	31.6
2	Area sample: HEPA filter exhaust (Operator Gary Roepke)	Dispense/Weigh 15 x 1 gm amounts of Naproxen Sodium from 100 gm container	37 mm, 1 µ GFF	2	0	58	58	3.013	2.951	2.98	172.8	4.14	24.0
3	Area sample: Transfer chamber (Operator Gary Roepke)	Dispense/Weigh 15 x 1 gm amounts of Naproxen Sodium from 100 gm container	37 mm, 1 µ GFF	3	0	58	58	3.021	2.935	2.98	172.8	4.54	26.3
4	Room sample (Operator Gary Roepke)	Dispense/Weigh 15 x 1 gm amounts of Naproxen Sodium from 100 gm container	37 mm, 1 µ GFF	4	0	58	58	3.02	2.969	2.99	173.4	2.83	16.3
5	Personal Sample: Breathing zone (Operator: Mike Rouse)	Dispense/Weigh 15 x 1 gm amounts of Naproxen Sodium from 100 gm container	37 mm, 1 µ GFF	1	0	63	63	2.986	2.886	2.94	185.2	3.56	19.2
6	Area Sample: HEPA filter exhaust (Operator: Mike Rouse)	Dispense/Weigh 15 x 1 gm amounts of Naproxen Sodium from 100 gm container	37 mm, 1 µ GFF	2	0	63	63	3.013	2.951	2.98	187.7	4.11	21.9
7	Area sample: Transfer chamber Operator (Mike Rouse)	Dispense/Weigh 15 x 1 gm amounts of Naproxen Sodium from 100 gm container	37 mm, 1 µ GFF	3	0	63	63	3.021	2.935	2.98	187.7	4.62	24.6
8	Room sample (Operator Mike Rouse)	Dispense/Weigh 15 x 1 gm amounts of Naproxen Sodium from 100 gm container	37 mm, 1 µ GFF	4	0	62	62	3.02	2.969	2.99	185.4	2.73	14.8
9	Personal Sample: Operator breathing zone (Operator: Bob Applequist)	Dispense/Weigh 15 x 1 gm amounts of Naproxen Sodium from 100 gm container	37 mm, 1 µ GFF	1	0	61	61	2.986	2.886	2.94	182.3	3.68	20.2
10	Area sample: HEPA filter exhaust (Operator Bob Applequist)	Dispense/Weigh 15 x 1 gm amounts of Naproxen Sodium from 100 gm container	37 mm, 1 µ GFF	2	0	61	61	3.013	2.951	2.98	181.7	3.56	19.6
11	Area sample: Transfer chamber (Bob Applequist)	Dispense/Weigh 15 x 1 gm amounts of Naproxen Sodium from 100 gm container	37 mm, 1 µ GFF	3	0	61	61	3.021	2.935	2.98	181.7	2.74	15.1
12	Room sample (Operator Bob Applequist)	Dispense/Weigh 15 x 1 gm amounts of Naproxen Sodium from 100 gm container	37 mm, 1 µ GFF	4	0	60	60	3.02	2.969	2.99	179.4	3.79	21.1
13	Corridor	Sample taken outside of test lab before and after weighings	37 mm, 1 µ GFF	4	0	57	57	3.02	2.969	2.99	170.6	3.83	22.5

Personal Protective Equipment: Lab coat, nitrile gloves
 Engineering Controls: Labconco Precise HEPA Filtered Glove Box
 Exposure limits: Surrogate monitoring with naproxen sodium. The occupational exposure limit (OEL) for naproxen sodium is 5 mg/m³

¹Pre and Post pump calibration with DC-Lite Primary Flow Meter[®]

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Industrial Hygiene Report
December 13, 2007

Industrial Hygiene Monitoring Laboratory Report
Precise HEPA-Filtered Glove Box

**Surrogate Air Monitoring for Naproxen Sodium
Summary of Personal Exposures
Weighing and Dispensing of 15 x 1-g amounts
@ Labconco Precise HEPA-Filtered Glove Box
December 13, 2007**

Sample No.	Sample Description	Round	Period (minutes)	Concentration (ng/m³)
1	Personal, G. Roepke, Operator 1, Project Engineer	1	58	31.6
5	Personal, M. Rouse, Operator 2, Engineering Technician	1	63	19.2
9	Personal, Bob Applequist, Operator 3, Product Manager	1	61	20.2

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Industrial Hygiene Report
December 13, 2007

Issued to: Gary Roepke
Labconco Corporation
8811 Prospect Avenue
Kansas City, Missouri 64132-2696

Compound: Naproxen Sodium
Data Report: SB897
Date: 12/26/07

DATA REPORT

CONCENTRATIONS OF NAPROXEN SODIUM ON SAMPLES COLLECTED AT LABCONCO

Distribution List:

G. Roepke, Labconco Corporation
M. Berkova, SafeBridge
T. Bryning, SafeBridge
File Copy, SafeBridge

ISSUED BY **SafeBridge Consultants, Inc.**
Analytical Laboratory
1924 Old Middlefield Way
Mountain View, CA 94043-2503
Phone: (650) 961-4820
Fax: (650) 623 0096

Disclaimer: This report must not be reproduced except in full unless approved by SafeBridge.

SB897

1 of 3


Compound: Naproxen Sodium
Data Report: SB897
Date: 12/26/07

DATA REPORT

SUMMARY INFORMATION:

1. Samples received: 12/14/07
2. Total number of samples received: 25
3. Number of samples analyzed: 25
4. Conditions of samples upon arrival: good, ambient
5. Storage conditions prior to analysis: ~ -20 ° C
6. Date range for sample extraction: 12/20/07
7. Method used for quantification: HPLC-FL
8. Quantitation Limit of the method: 2 ng of Naproxen Sodium per sample

Report prepared by:




M. Berkova, PhD.
Senior Chemist I




Date

Report checked by:



T. Bryning, M.S.
Principal Chemist



Date

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 Labconco Corp.
 Industrial Hygiene Report
 December 13, 2007

SAMPLE RESULTS FROM INDUSTRIAL HYGIENE MONITORING

Sampling Location*: Labconco Corporation
 Sample Collected by: Larry Hambleton, Consultant, Labconco Corp.
 Analytical Chemist: Market Berkova
 Data Report Number: SB897
 Notebook Reference: 2007-7 p. 78

DATE SAMPLED*	SAMPLING DEVICE* ¹	SAMPLE ID*	ANALYTE*	AMOUNT OF ANALYTE # ng/cassette	AIR VOLUME L*	CONC. OF ANALYTE ng/m ³	ANALYTICAL METHOD
12/13/2007	GFF ¹	1	Naproxen Sodium	5.39	170.5	31.6	HPLC-FL
12/13/2007	GFF	2	Naproxen Sodium	4.15	172.8	24.0	HPLC-FL
12/13/2007	GFF	3	Naproxen Sodium	4.54	172.8	26.3	HPLC-FL
12/13/2007	GFF	4	Naproxen Sodium	2.83	173.4	16.3	HPLC-FL
12/13/2007	GFF	5	Naproxen Sodium	3.56	185.2	19.2	HPLC-FL
12/13/2007	GFF	6	Naproxen Sodium	4.12	187.7	21.9	HPLC-FL
12/13/2007	GFF	7	Naproxen Sodium	4.61	187.7	24.6	HPLC-FL
12/13/2007	GFF	8	Naproxen Sodium	2.74	185.4	14.8	HPLC-FL
12/13/2007	GFF	9	Naproxen Sodium	3.68	182.3	20.2	HPLC-FL
12/13/2007	GFF	10	Naproxen Sodium	3.56	181.7	19.6	HPLC-FL
12/13/2007	GFF	11	Naproxen Sodium	2.74	181.7	15.1	HPLC-FL
12/13/2007	GFF	12	Naproxen Sodium	3.79	179.4	21.1	HPLC-FL
12/13/2007	GFF	13	Naproxen Sodium	3.84	170.6	22.5	HPLC-FL

¹GFF – Glass Fiber Filter, 37 mm in Polystyrene cassette

Quantitation limit for Naproxen sodium is 2 ng/sample

*information provided by client

Data not corrected for blank. Amount found on blank QC was BQL

Results relate only to the items tested



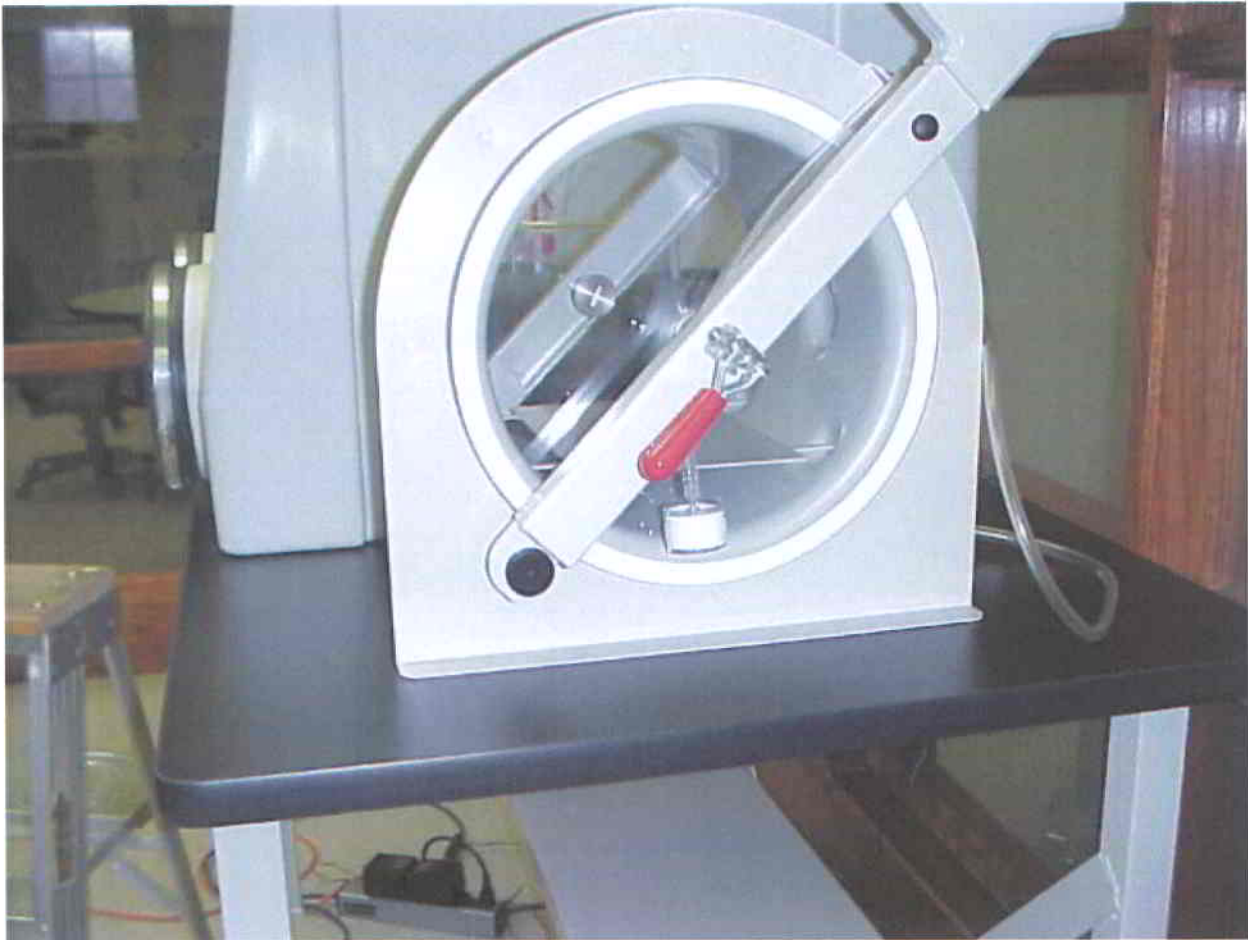
Precise HEPA-Filtered Glove Box



Collar Sampling Cassette



HEPA Filter Sampling Location



Transfer Sampling Location



Spillage from Operator #1



Operator #2 Weighing Technique (note wet towels to contain spills)