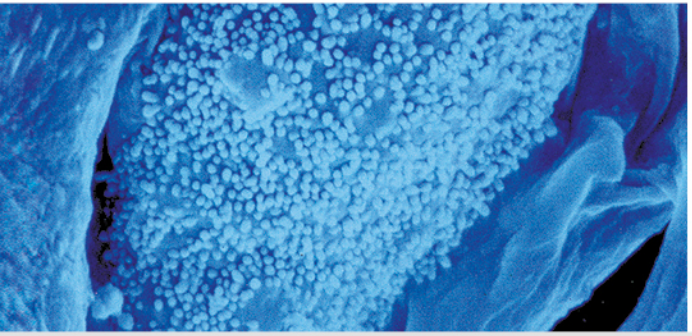
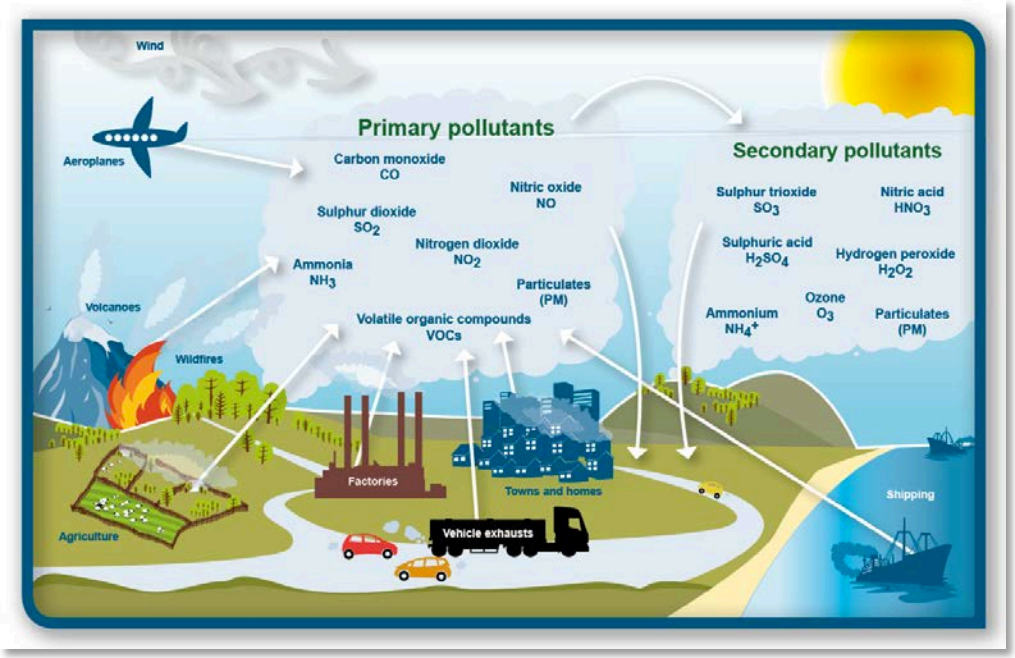
Cutting-edge *in vitro* Exposure Technologies for Conventional and E-cigarettes

IIVS Workshop
In Vitro Exposure Systems and Dosimetry Assessment Tools for Inhaled Tobacco Products
April 4-6, 2016



VITROCELL® SYSTEMS

Gases
Complex Mixtures
Airborne Particles (Nano Particles)

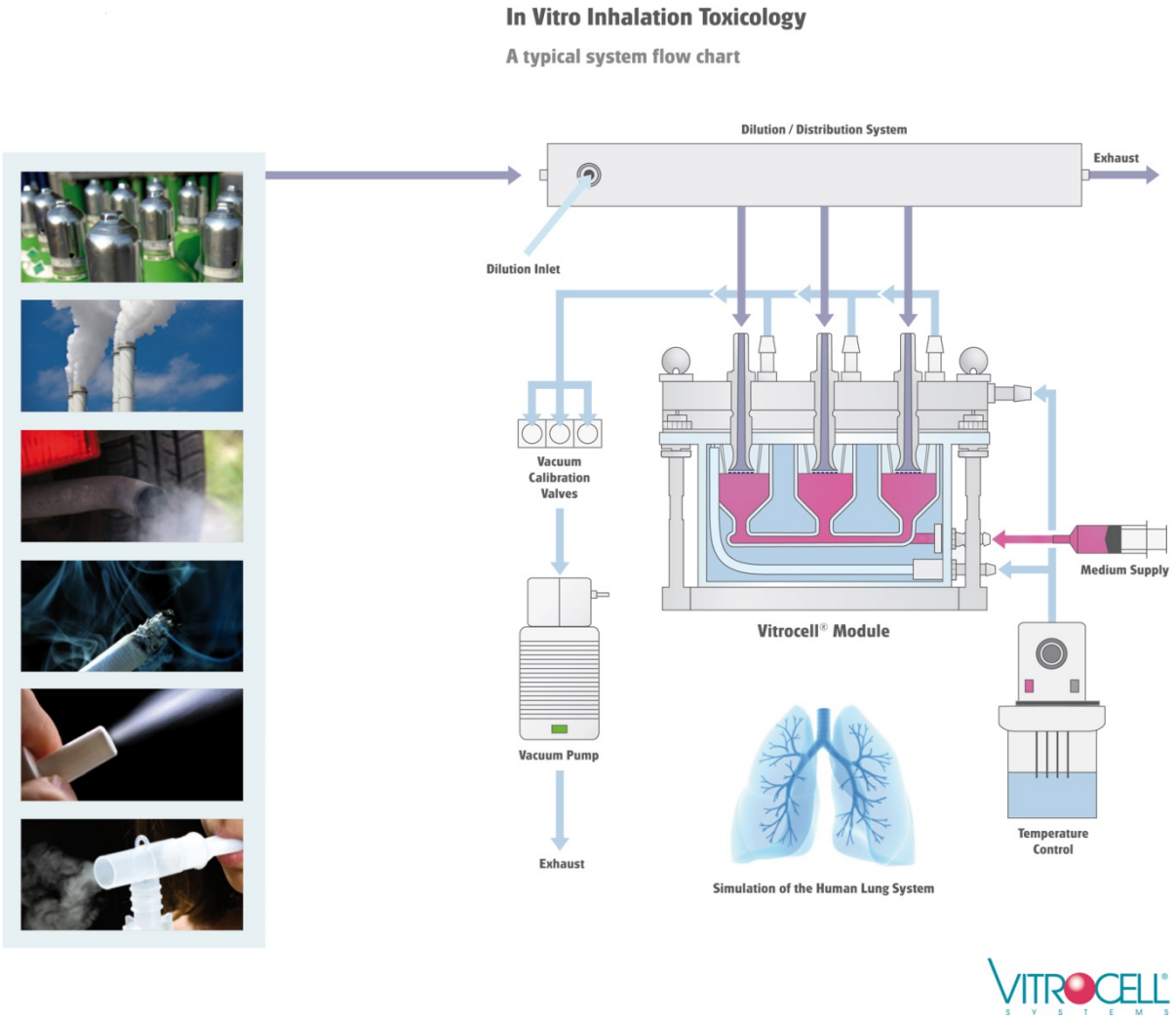


source: environment.scotland.gov.uk

source: cysticfibrosisnewstoday.com

Our mission: to provide turnkey in vitro exposure systems incl. online dosimetry tools

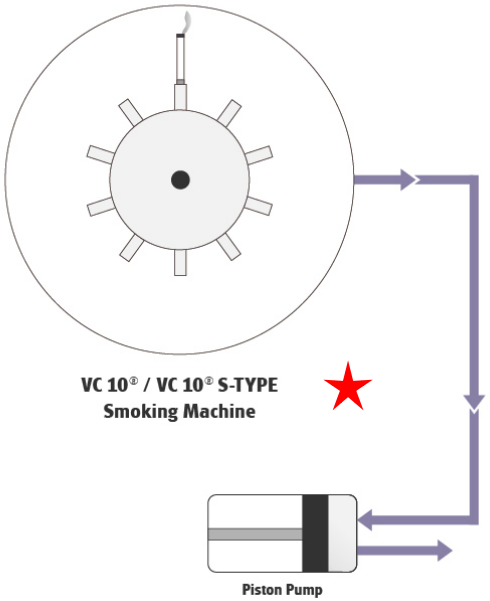
VITROCELL® Continuous Flow System



Critical System Elements for *in vitro* Exposure to Conventional and E-cigarettes

	Conventional	E-cigarette
• Smoke / Vapor generation		
– Smoking regimen	ISO/HCI Bell	55/70 mL 30s/3s Square
– Actuation	Lighter	Draw / Button
• Dilution for dose / response		
– Typical concentration ranges	5 - 50% Smoke	30 – 80% Aerosol
• Exposure system	same	
• Auxiliary equipment	ISO Lab Conditions	Evtl. Heated Chambers
• Dosimetry tools		
– Gas phase	Chemical Analysis	Chemical Analysis
	CO	-
	TOF-MS	TOF-MS
– Particle phase	Chemical Analysis	Chemical Analysis
	Photometer	Photometer
	Microbalance	Microbalance

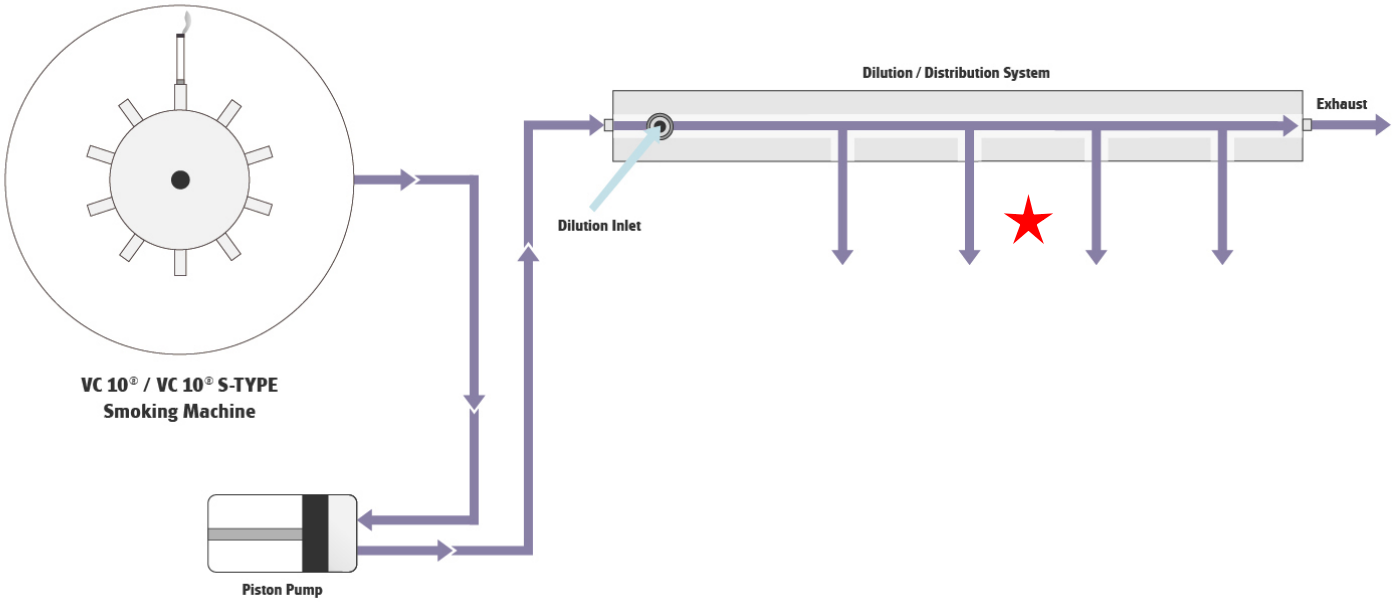
System Element: Smoke / Vapor Generation



Hotspot: ★

- Reproducible aerosol generation with smallest dead volumes
- Avoidance of cross-contamination when testing different products
- Fast and easy cleaning

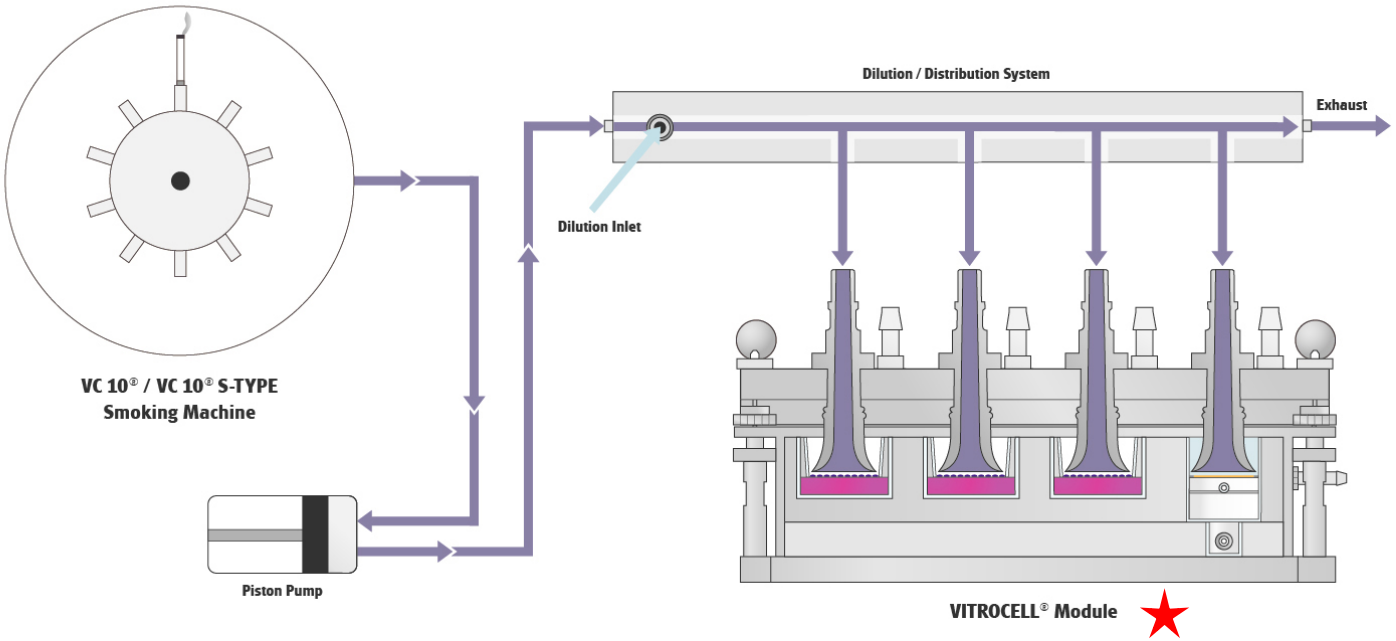
System Element: Dilution System



Hotspot: ★

- Reproducible dynamic dilution with smallest dead volumes
- „Fresh aerosol“ with quick delivery to test system
- Easy cleaning

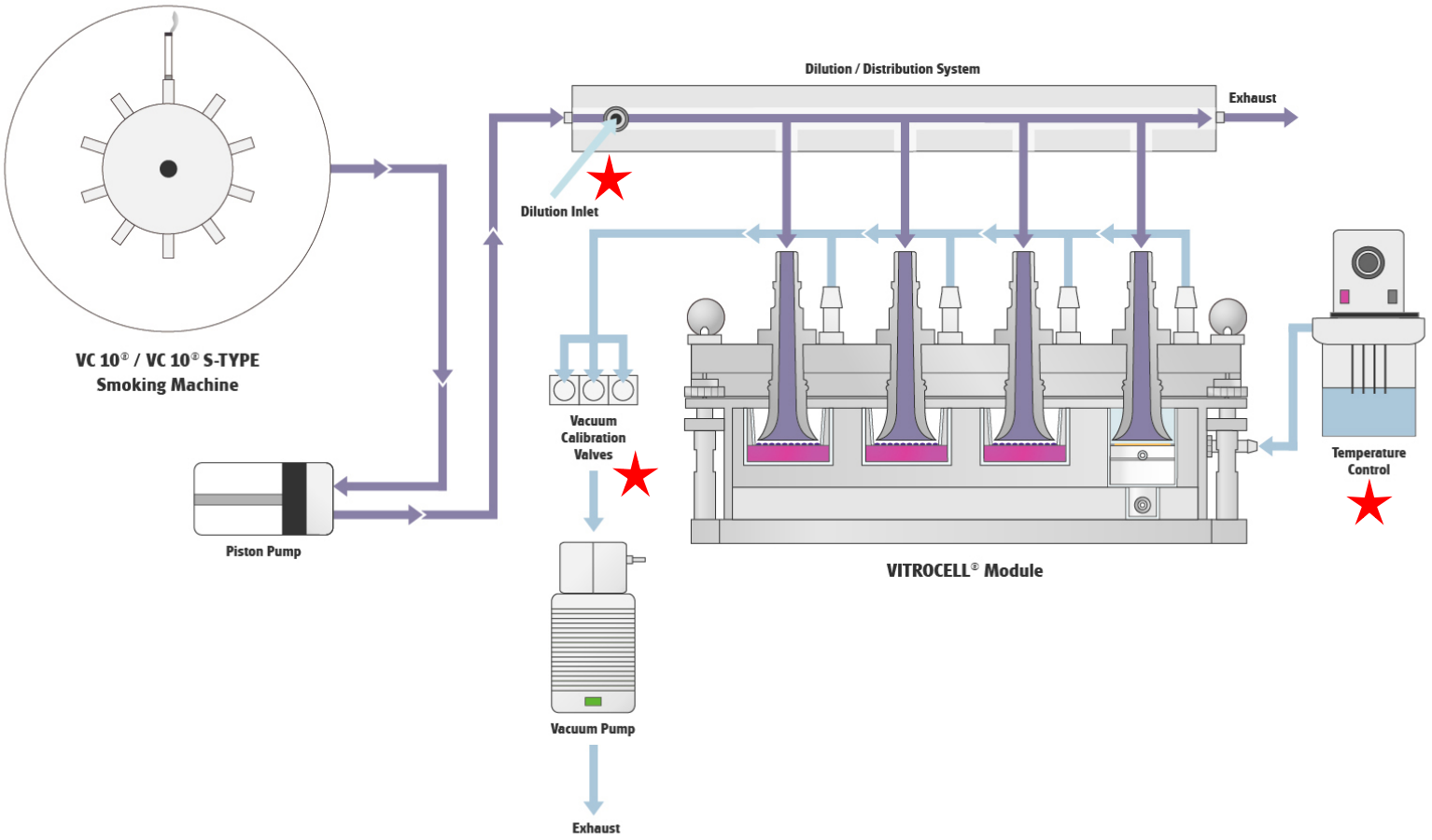
System Element: Exposure Module



Hotspot: ★

- Receipt of fresh aerosol / Air-Liquid Interface
- Uniform particle deposition
- Easy cleaning and reliable operation

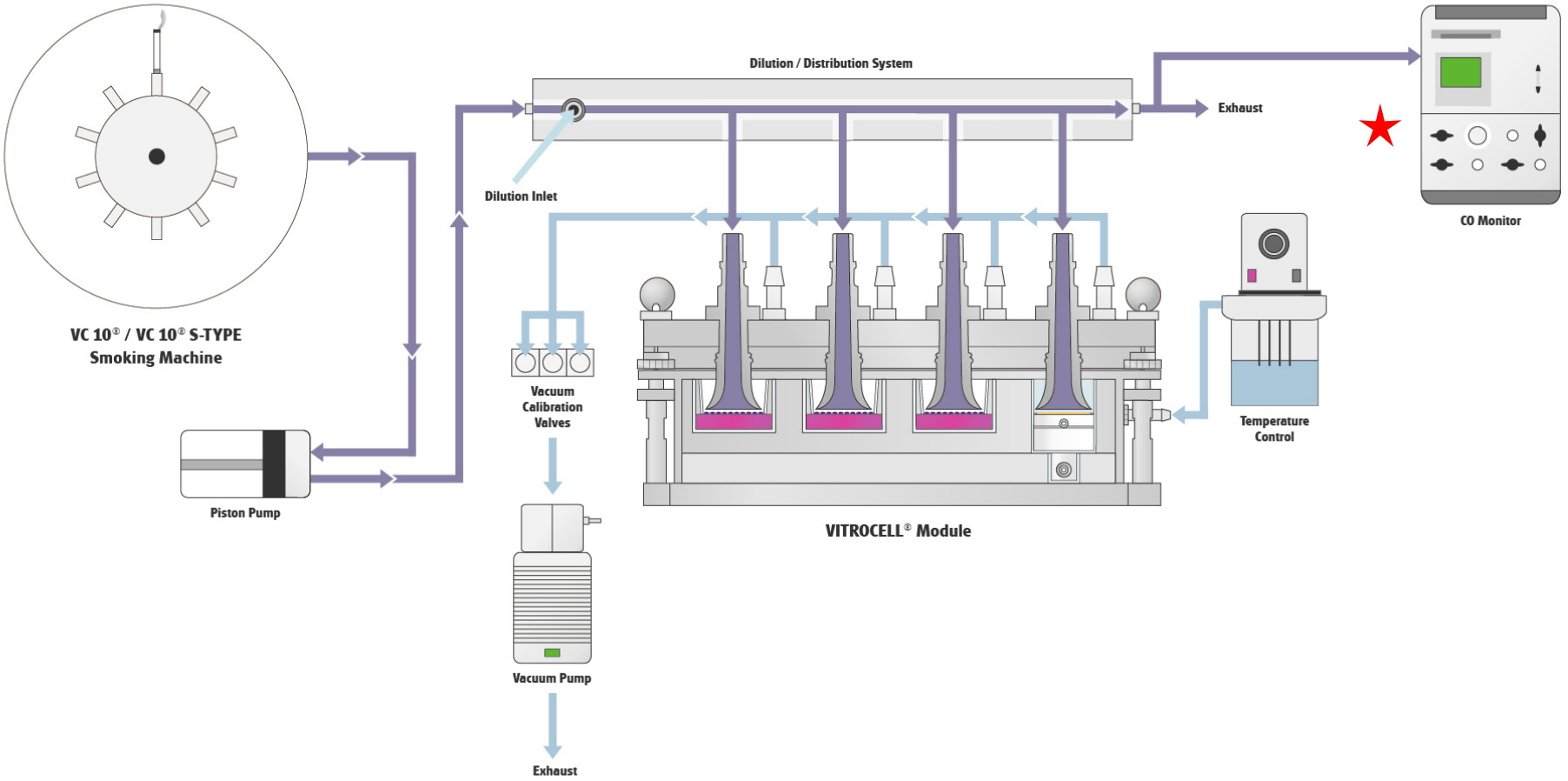
System Element: Auxiliary Equipment



Hotspot: ★

- Heating / maintain constant exposure conditions
- Manage constant dilution air flow rates
- Manage constant vacuum flow rates

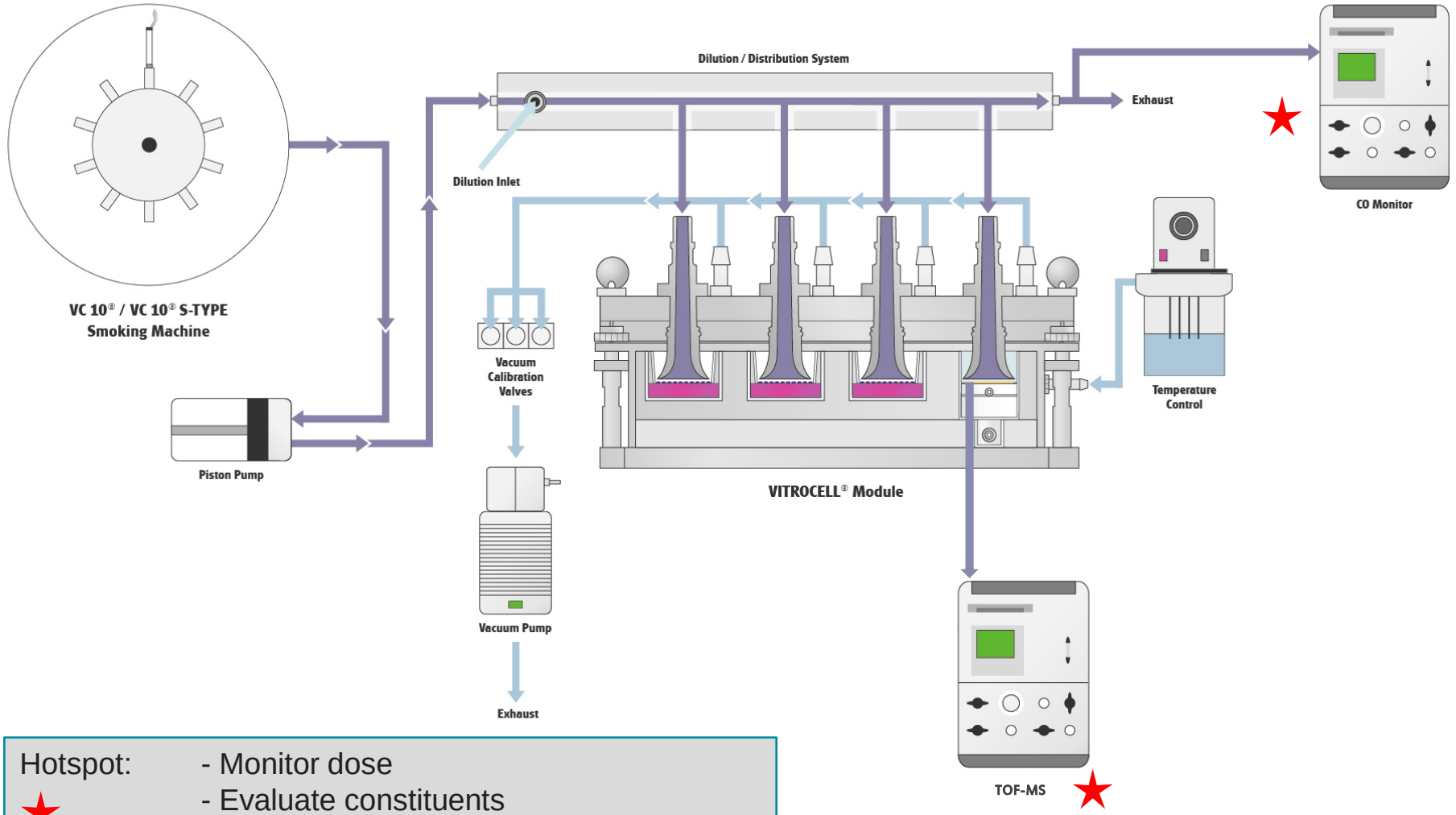
System Element: Online Gas Phase Dosimetry Tools



Hotspot: ★

- Monitor Dose
- Evaluate Dose
- No disturbance of exposure process

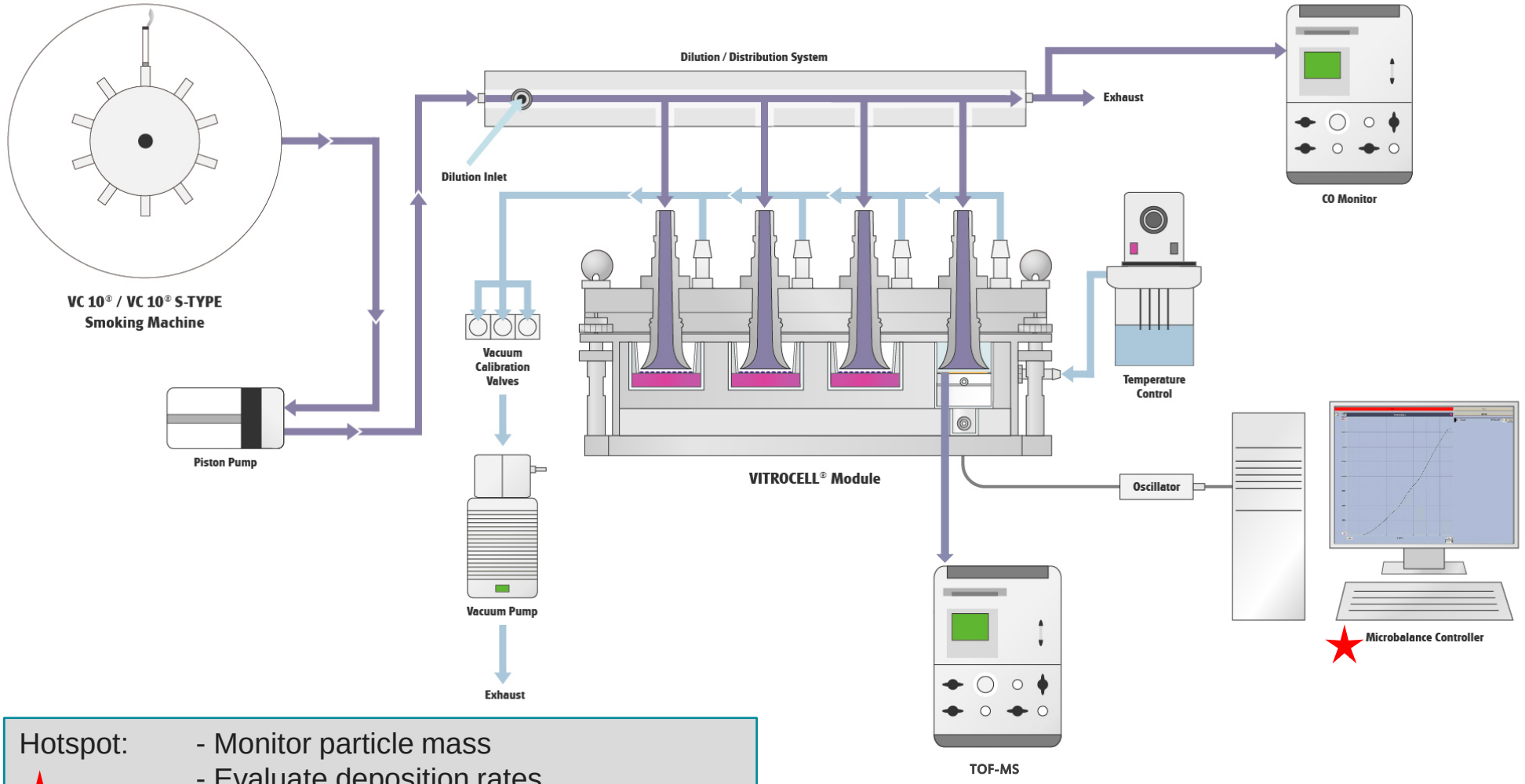
System Element: Online Gas Phase Dosimetry Tools



Hotspot: ★

- Monitor dose
- Evaluate constituents
- No interference with exposure process

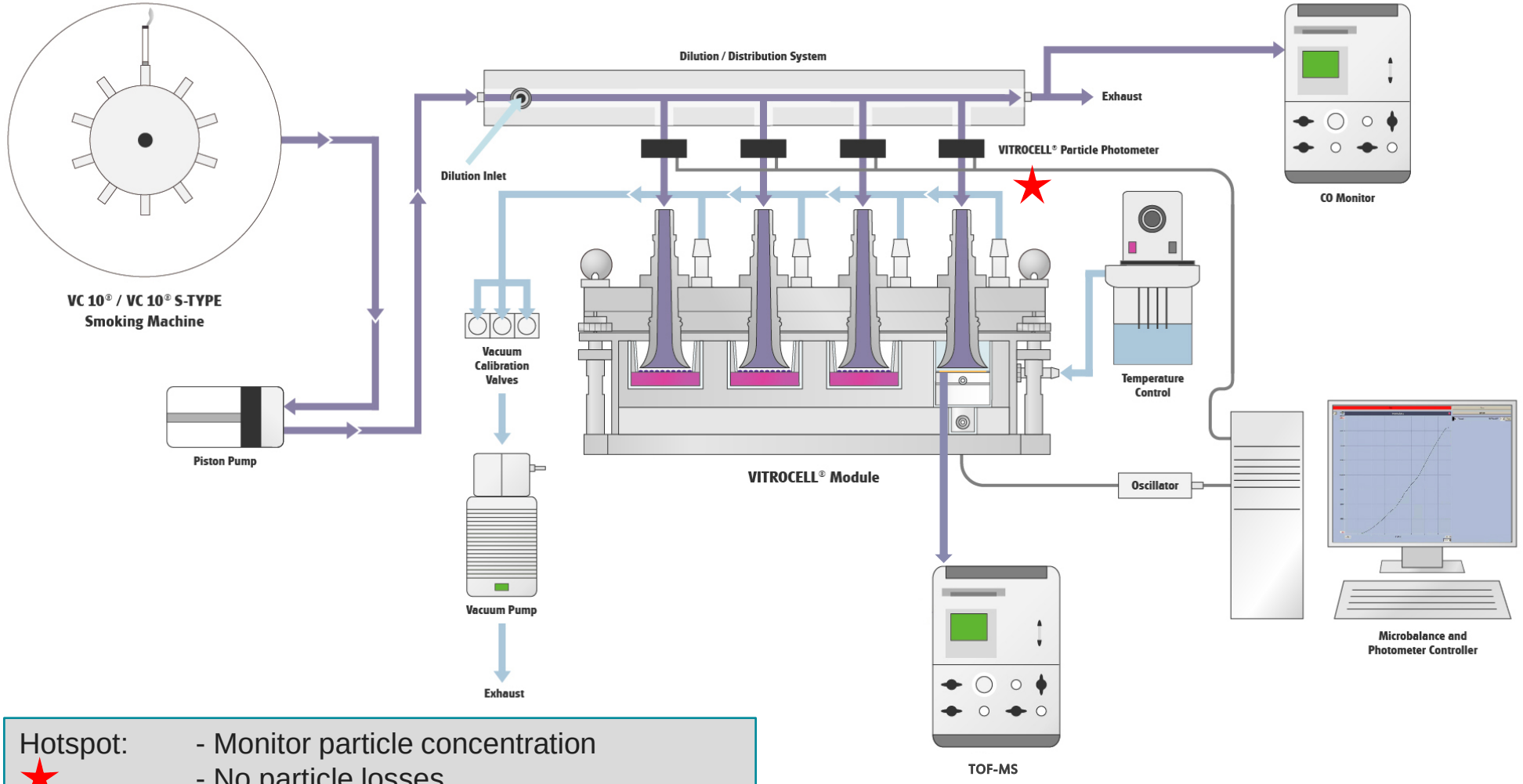
System Element: Dosimetry Particle Deposition via Quartz Crystal Microbalances



Hotspot: ★

- Monitor particle mass
- Evaluate deposition rates
- No disturbance of exposure process

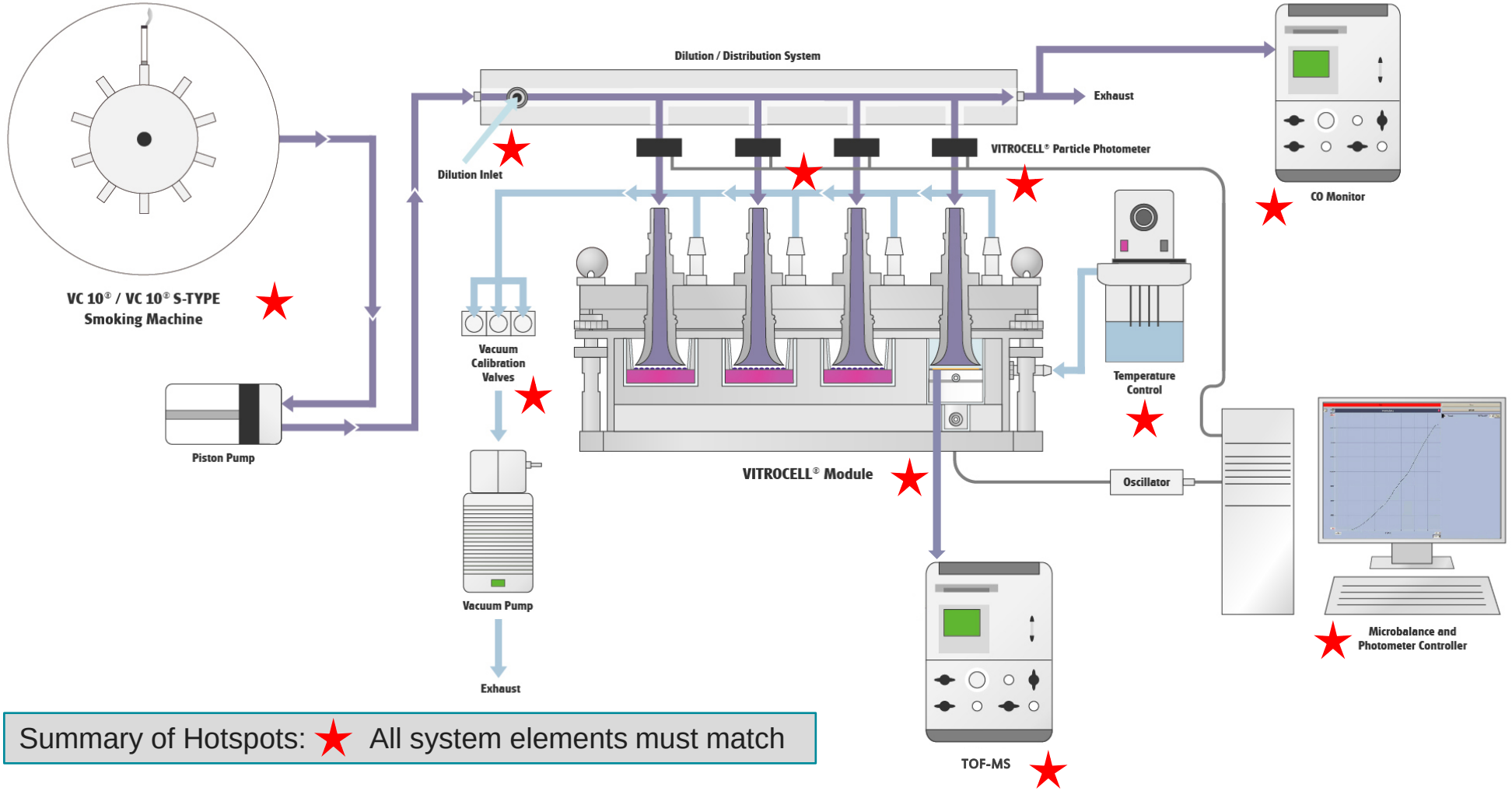
System Element: Dosimetry Particle Concentration via Inline Photometers



Hotspot: ★

- Monitor particle concentration
- No particle losses
- No disturbance of exposure process

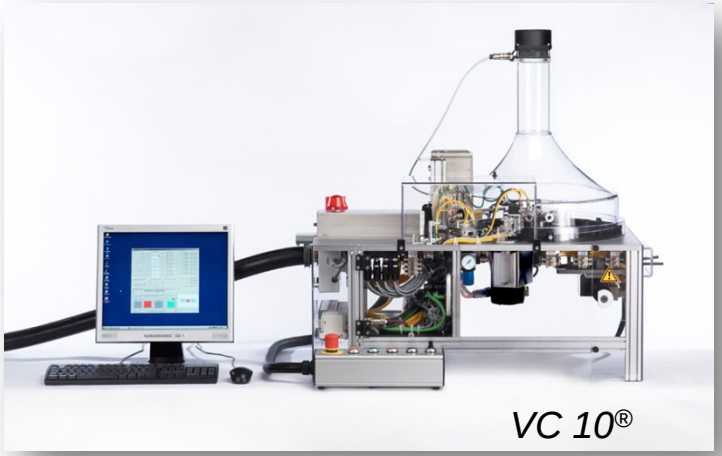
The Complete Exposure System



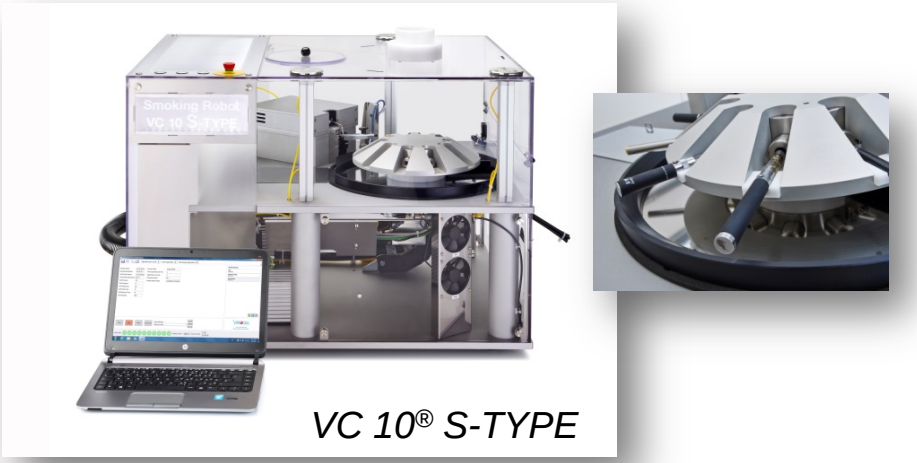
Summary of Hotspots: ★ All system elements must match

System Element: Smoke / Vapor Generation

Automatic Robots



VC 10®



VC 10® S-TYPE

Manual Machines

VC 1

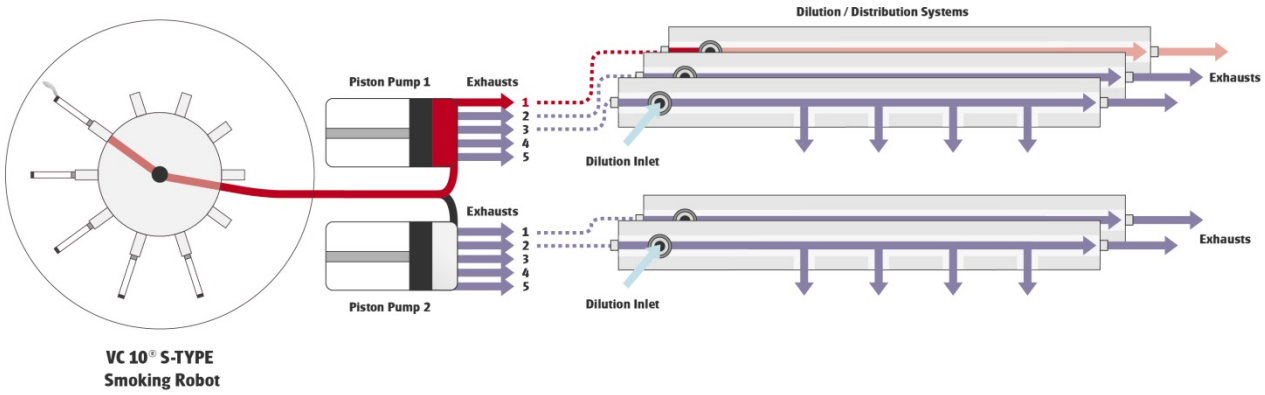
VC 1 Linear Type

Vapestarter

System Element: Smoke / Vapor Generation
Automatic Robots

VC 10® S-TYPE

- Smallest dead volume
- Conventional and e-cigarettes
- Fast and easy cleaning
- Product change in < 10 min. (exchange parts)
- Increased capacity via multiple pumps

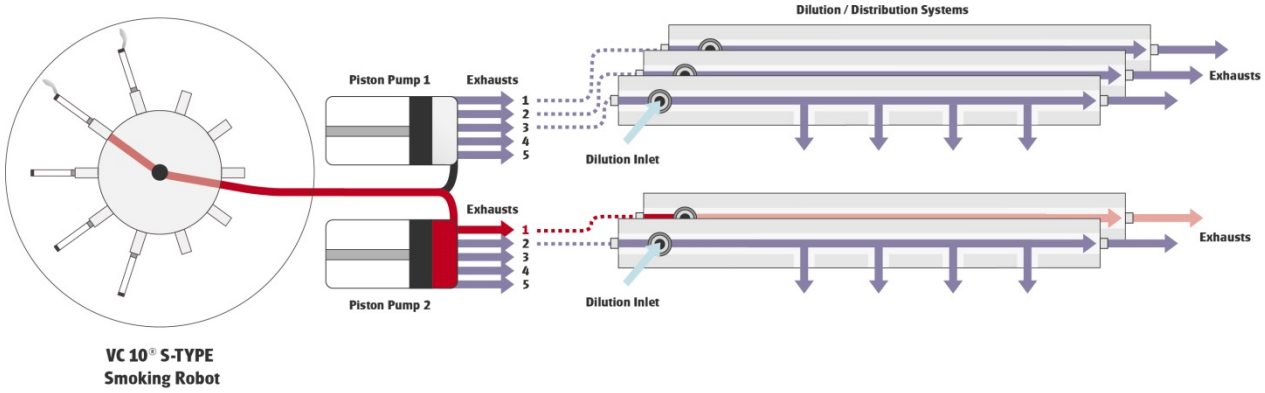


VC 10® S-TYPE
Smoking Robot

System Element: Smoke / Vapor Generation Automatic Robots

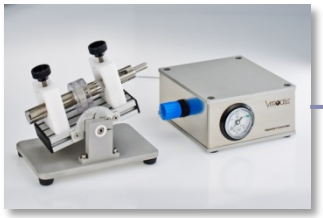
VC 10® S-TYPE

- Smallest dead volume
- Conventional and e-cigarettes
- Fast and easy cleaning
- Product change in < 10 min. (exchange parts)
- Increased capacity via multiple pumps



VC 10® S-TYPE
Smoking Robot

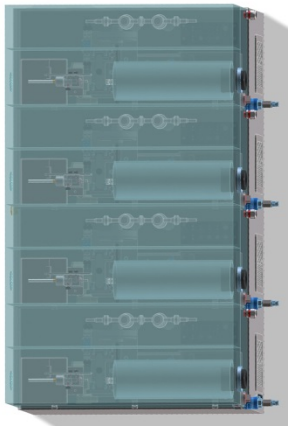
System Element: Smoke / Vapor Generation Manual Machines

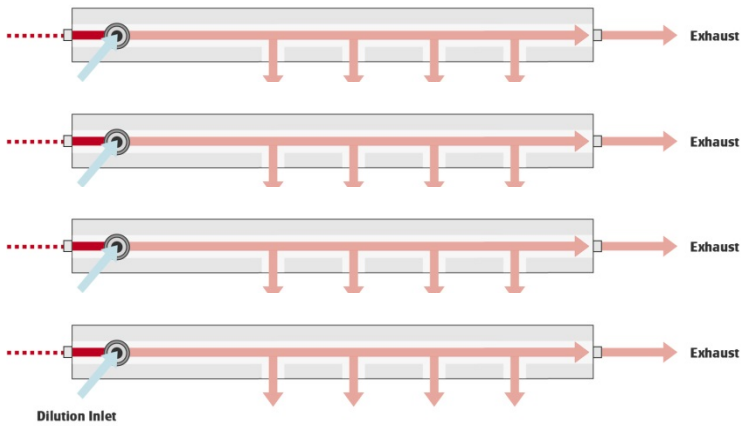


Vapestarter

VC 1 Linear Type

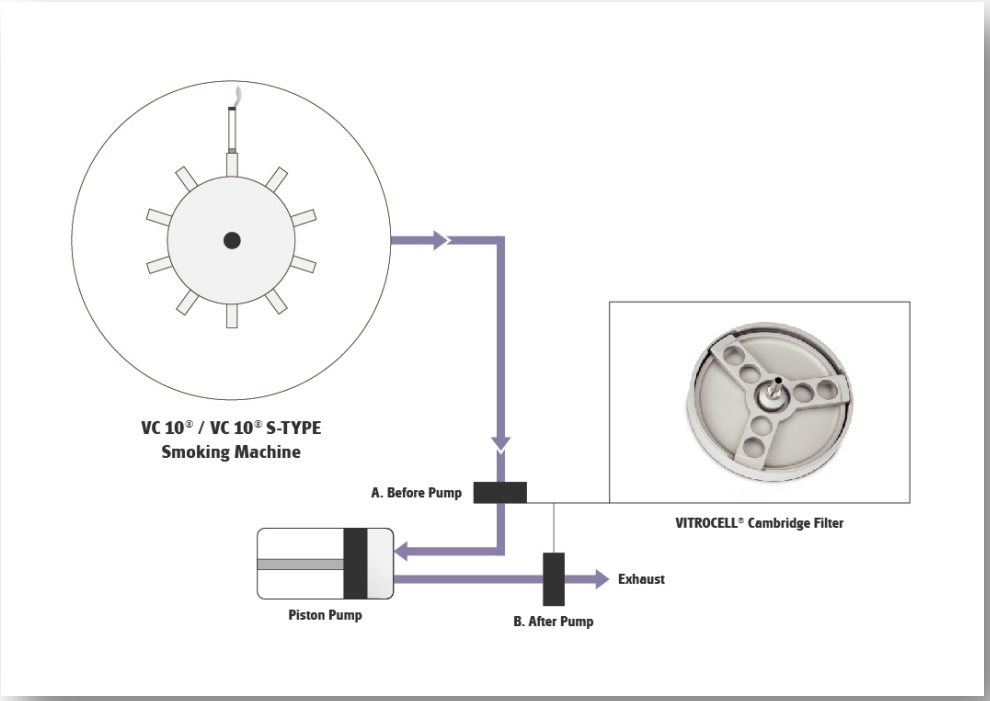
- Smallest dead volumes
- (Conventional) and e-cigarettes
- Fast and easy cleaning
- Increased capacity via multiple pumps
- Run positive control in same experiment





System Element: Smoke / Vapor Generation

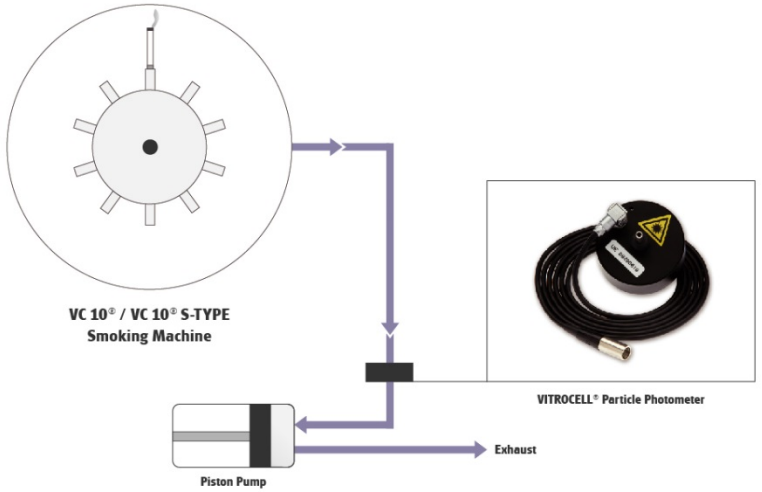
TPM Collection on 92 mm Cambridge Filter Pad before and after Syringe Pump

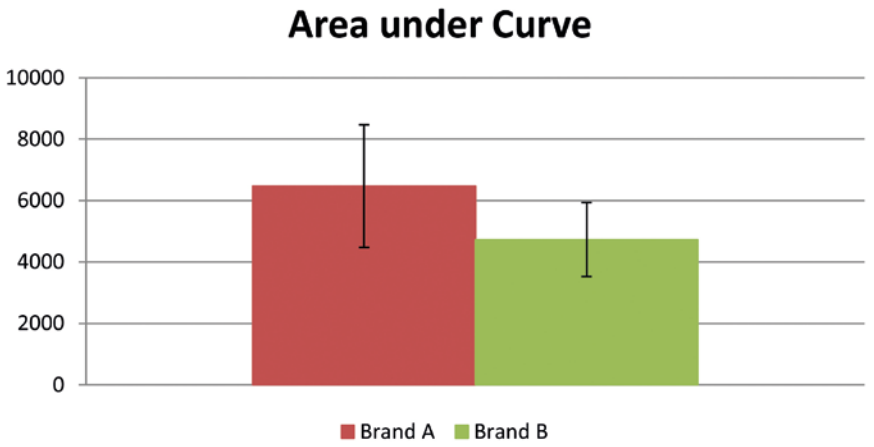


- VC 10 S-TYPE
- 20 cigarettes 3R4F/run
- ISO regime, 8 puffs

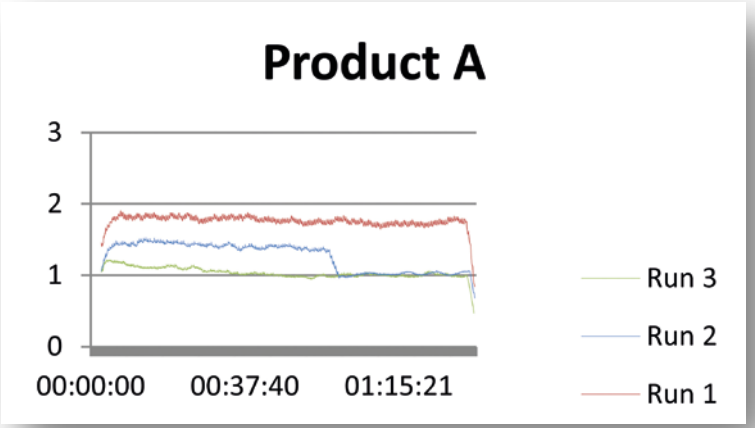
System Element: E-cigarette Vapor Generation

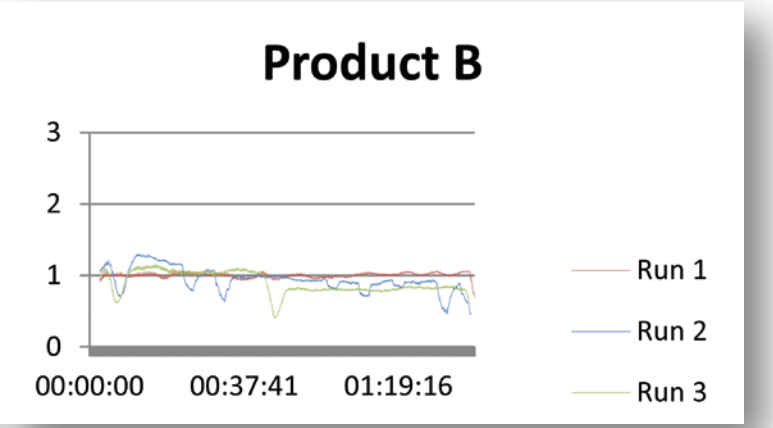
Detection of aerosol concentration



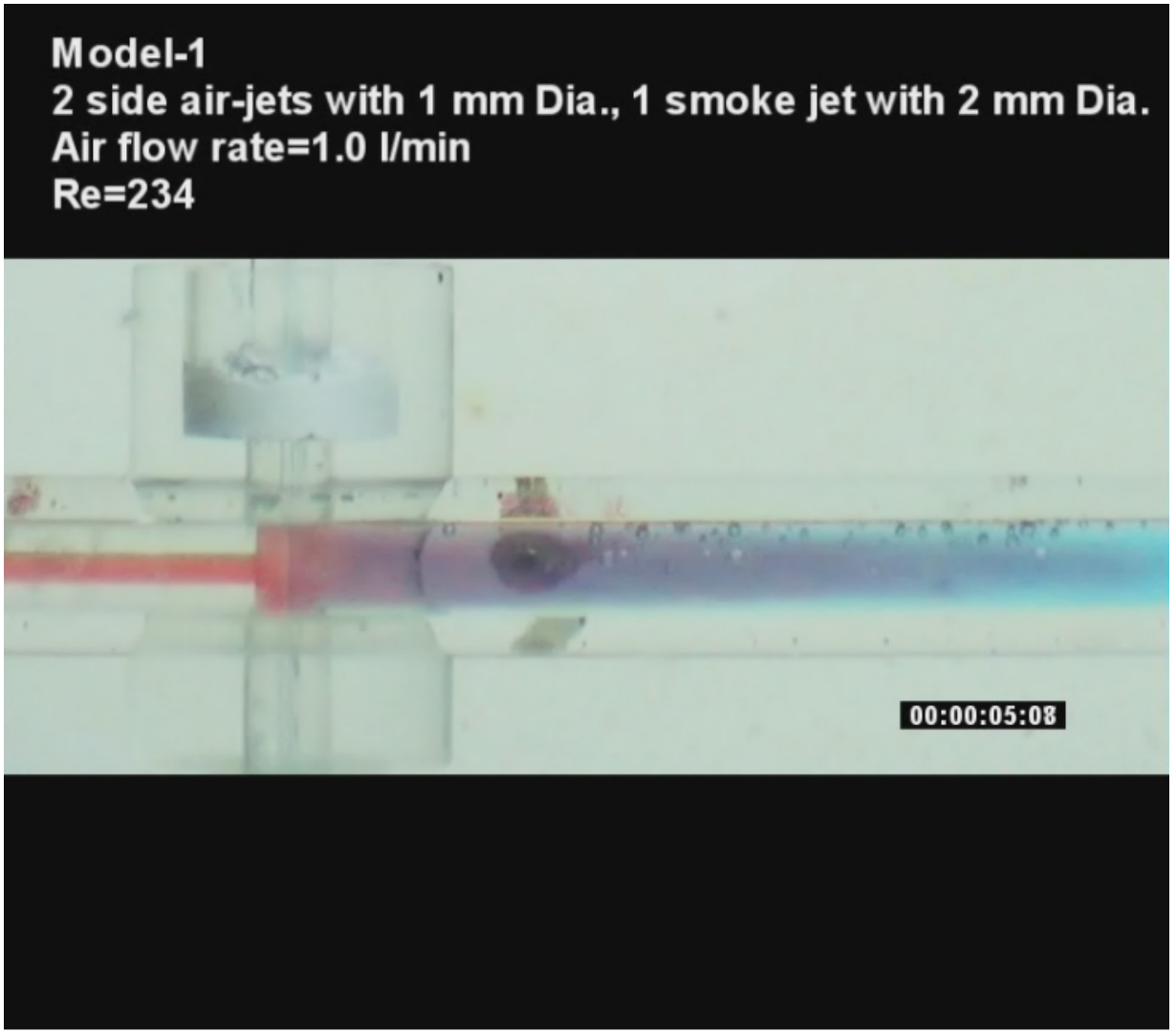


- VC 10 S-TYPE
- Draw actuated product
- 3 runs,180 puffs,
- 50 mL square profile
- 3 s duration
- 30 s frequency



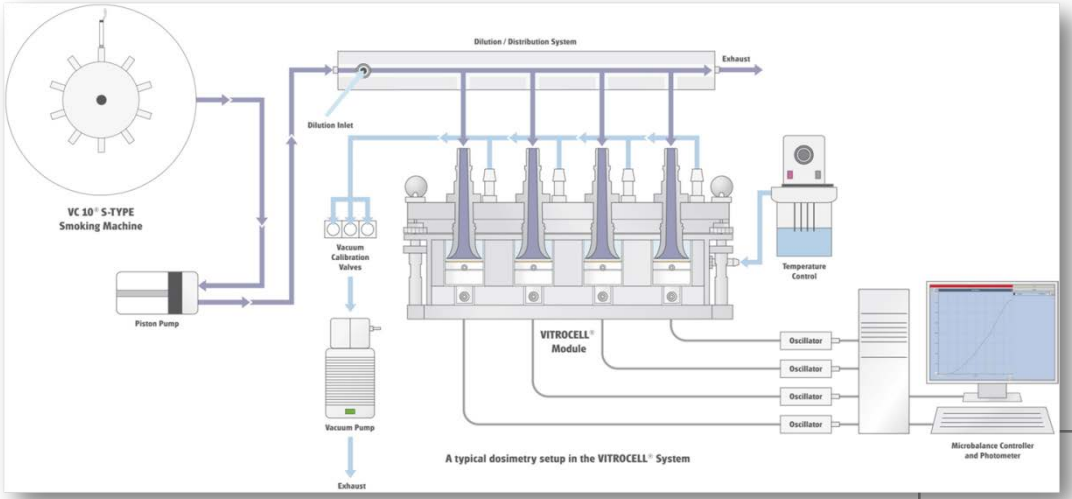


System Element: Dilution System



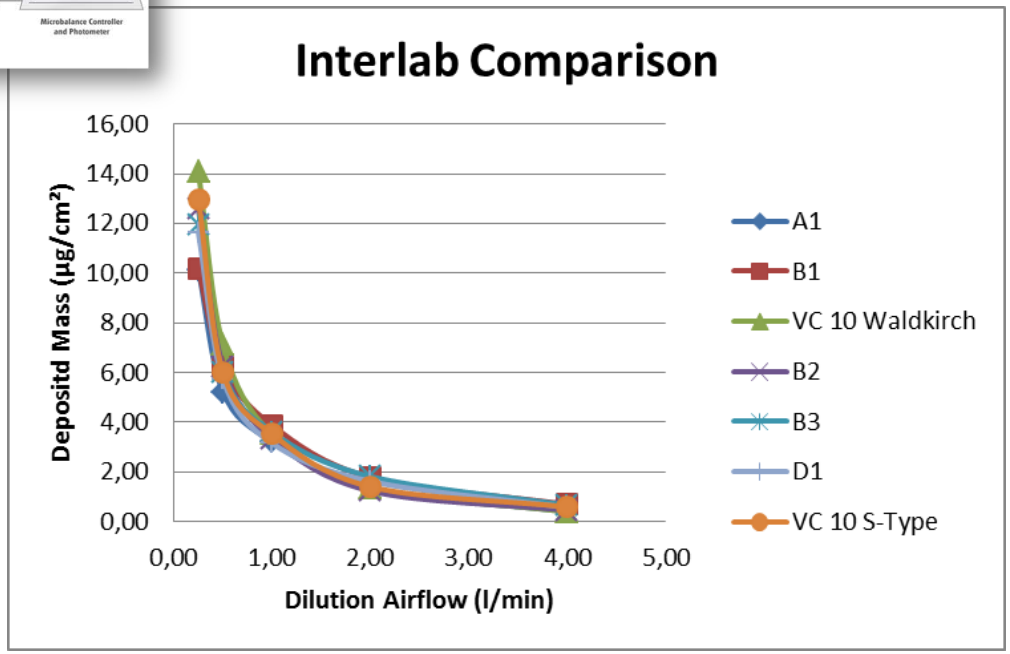
System Element: Smoke / Vapor Generation & Dilution Systems

Smoking machine, dilution and exposure system validation via Quartz Crystal Microbalances



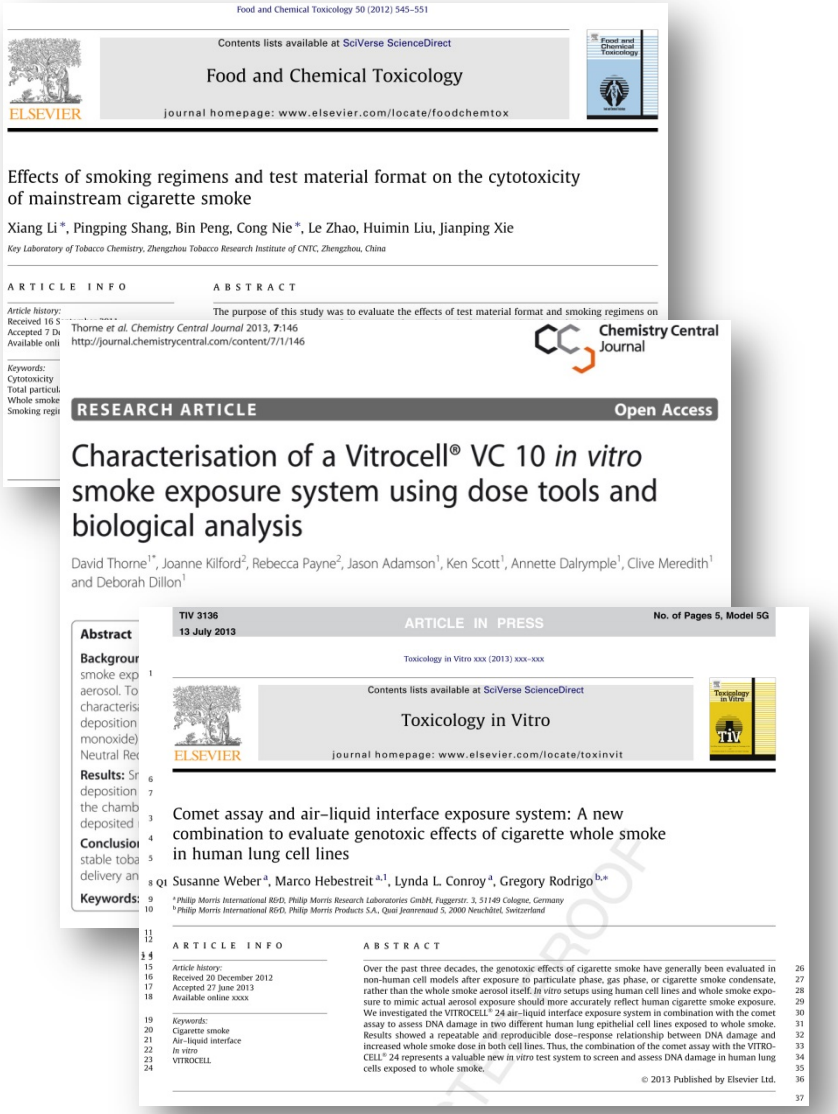
- Average of 5 runs 20 cigarettes 3R4F
- ISO regime, 8 puffs

Standard Deviation in µg/cm2					
Dilution Flow (l/min)	0,25	0,5	1	2	4
VC 10 S-Type	2,72	0,47	0,15	0,01	0,02
VC 10 Average	2,68	0,64	0,35	0,18	0,09
A1	1,72	0,5	0,37	0,22	0,06
B1	1,02	0,46	0,21	0,12	0,12
VC 10 Waldkirch	4,55	1,32	0,55	0,24	0,08
B2	2,68	0,62	0,34	0,2	0,13
B3	3,42	0,3	0,27	0,12	0,07
D1	1,15	0,54	0,18	0,11	0,1



Smoking Robot VC 10®

The most characterised smoking machine for *in vitro* applications



Food and Chemical Toxicology 50 (2012) 545–551

Contents lists available at SciVerse ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Effects of smoking regimens and test material format on the cytotoxicity of mainstream cigarette smoke

Xiang Li *, Pingping Shang, Bin Peng, Cong Nie *, Le Zhao, Huimin Liu, Jianping Xie

Key Laboratory of Tobacco Chemistry, Zhengzhou Tobacco Research Institute of CNTC, Zhengzhou, China

ARTICLE INFO

ABSTRACT

The purpose of this study was to evaluate the effects of test material format and smoking regimens on

Thorne et al. Chemistry Central Journal 2013, 7:146

http://journal.chemistrycentral.com/content/7/1/146

Chemistry Central Journal

RESEARCH ARTICLE Open Access

Characterisation of a Vitrocell® VC 10 *in vitro* smoke exposure system using dose tools and biological analysis

David Thorne[1*], Joanne Kilford[2], Rebecca Payne[2], Jason Adamson[1], Ken Scott[1], Annette Dalrymple[1], Clive Meredith[1] and Deborah Dillon[1]

Abstract

Backgrou

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Neutral Re

Results: Sr

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Conclusio

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Keywords:

TIV 3136 ARTICLE IN PRESS No. of Pages 5, Model 5G

13 July 2013

Toxicology in Vitro xxx (2013) xxx–xxx

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Toxicology in Vitro

journal homepage: www.elsevier.com/locate/toxinvit

Comet assay and air–liquid interface exposure system: A new combination to evaluate genotoxic effects of cigarette whole smoke in human lung cell lines

Susanne Weber [a], Marco Hebestreit [a,1], Lynda L. Conroy [a], Gregory Rodrigo [b,*]

[a] Philip Morris International R&D, Philip Morris Research Laboratories GmbH, Fuggerstr. 3, 51149 Cologne, Germany

[b] Philip Morris International R&D, Philip Morris Products S.A., Quai Jeanrenaud 5, 2000 Neuchâtel, Switzerland

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Cigarette smoke
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VITROCELL

ABSTRACT

Over the past three decades, the genotoxic effects of cigarette smoke have generally been evaluated in non-human cell models after exposure to particulate phase, gas phase, or cigarette smoke condensate, rather than the whole smoke aerosol itself. *In vitro* setups using human cell lines and whole smoke exposure to mimic actual aerosol exposure should more accurately reflect human cigarette smoke exposure. We investigated the VITROCELL® 24 air–liquid interface exposure system in combination with the comet assay to assess DNA damage in two different human lung epithelial cell lines exposed to whole smoke. Results showed a repeatable and reproducible dose–response relationship between DNA damage and increased whole smoke dose in both cell lines. Thus, the combination of the comet assay with the VITROCELL® 24 represents a valuable new *in vitro* test system to screen and assess DNA damage in human lung cells exposed to whole smoke.

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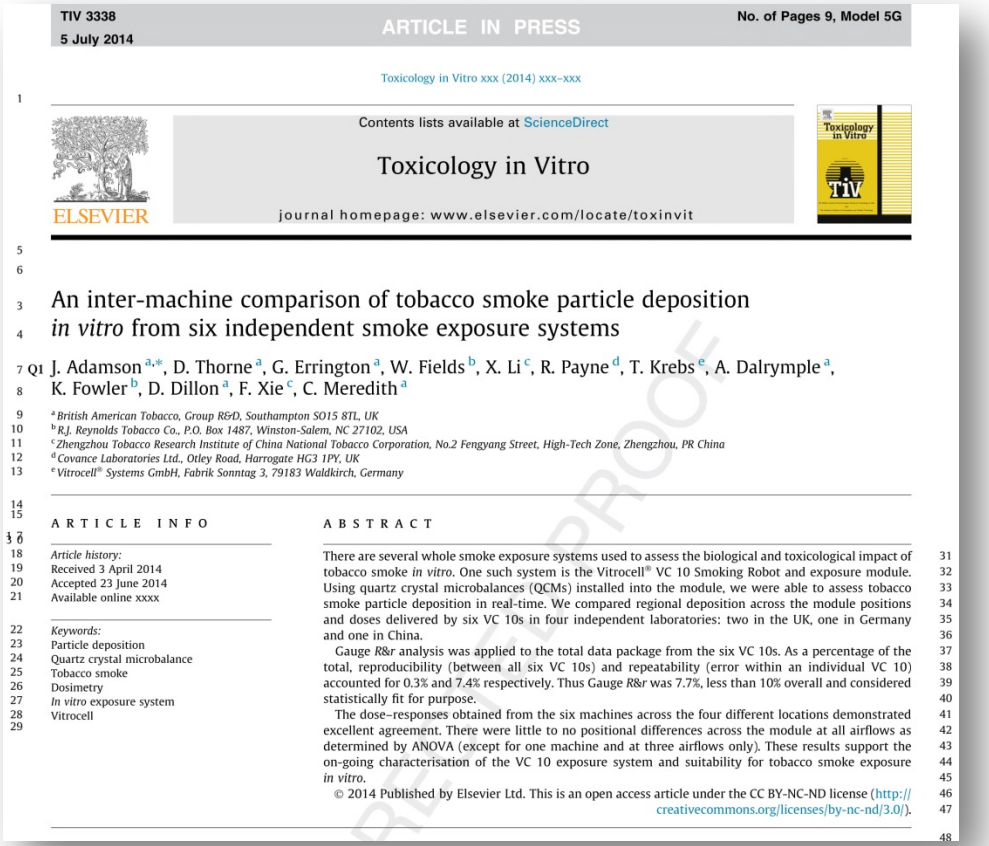

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Contents lists available at ScienceDirect

Toxicology in Vitro

journal homepage: www.elsevier.com/locate/toxinvit

An inter-machine comparison of tobacco smoke particle deposition *in vitro* from six independent smoke exposure systems

J. Adamson [a,*], D. Thorne [a], G. Errington [a], W. Fields [b], X. Li [c], R. Payne [d], T. Krebs [e], A. Dalrymple [a], K. Fowler [b], D. Dillon [a], F. Xie [c], C. Meredith [a]

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Particle deposition
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Tobacco smoke
Dosimetry
In vitro exposure system
Vitrocell

ABSTRACT

There are several whole smoke exposure systems used to assess the biological and toxicological impact of tobacco smoke *in vitro*. One such system is the Vitrocell® VC 10 Smoking Robot and exposure module. Using quartz crystal microbalances (QCMs) installed into the module, we were able to assess tobacco smoke particle deposition in real-time. We compared regional deposition across the module positions and doses delivered by six VC 10s in four independent laboratories: two in the UK, one in Germany and one in China.

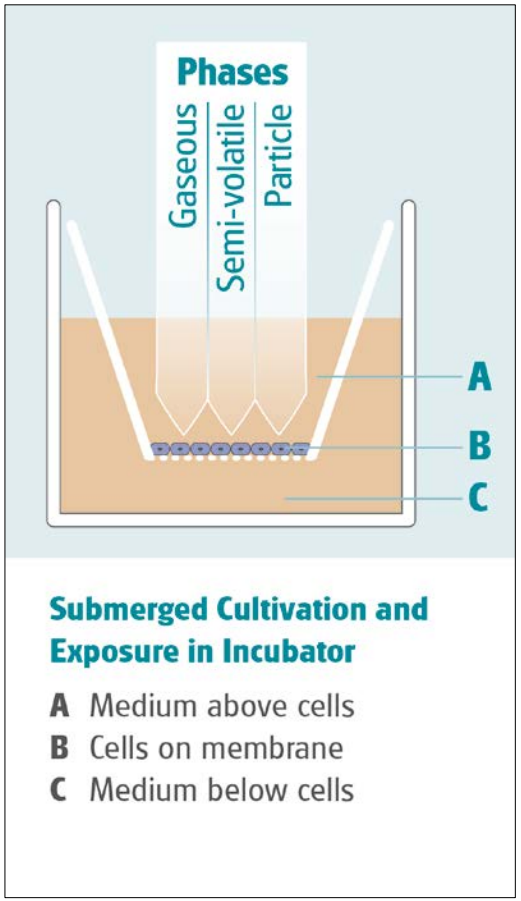
Gauge R&r analysis was applied to the total data package from the six VC 10s. As a percentage of the total, reproducibility (between all six VC 10s) and repeatability (error within an individual VC 10) accounted for 0.3% and 7.4% respectively. Thus Gauge R&r was 7.7%, less than 10% overall and considered statistically fit for purpose.

The dose–responses obtained from the six machines across the four different locations demonstrated excellent agreement. There were little to no positional differences across the module at all airflows as determined by ANOVA (except for one machine and at three airflows only). These results support the on-going characterisation of the VC 10 exposure system and suitability for tobacco smoke exposure *in vitro*.

A few sample publications

System Element: Exposure Module

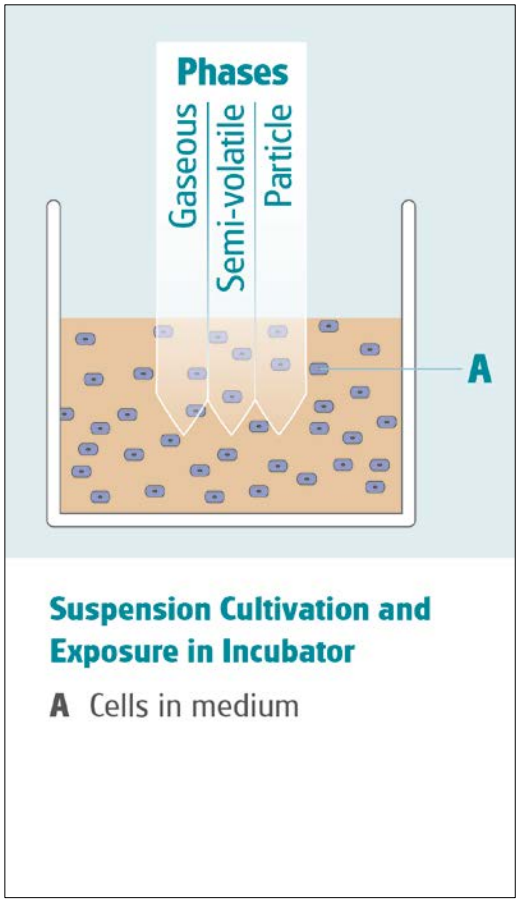
Advantages of exposure at the Air/Liquid Interface (ALI)



Submerged Cultivation and Exposure in Incubator

A Medium above cells
B Cells on membrane
C Medium below cells

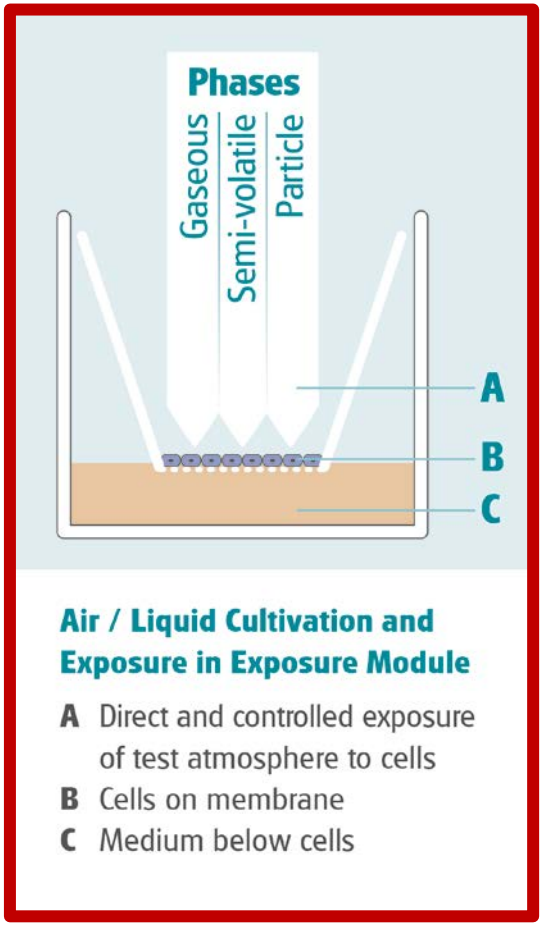
Submerged Exposure
Low Sensitivity
Undefined Dose



Suspension Cultivation and Exposure in Incubator

A Cells in medium

Exposure in Suspension
Low Sensitivity
Undefined Dose



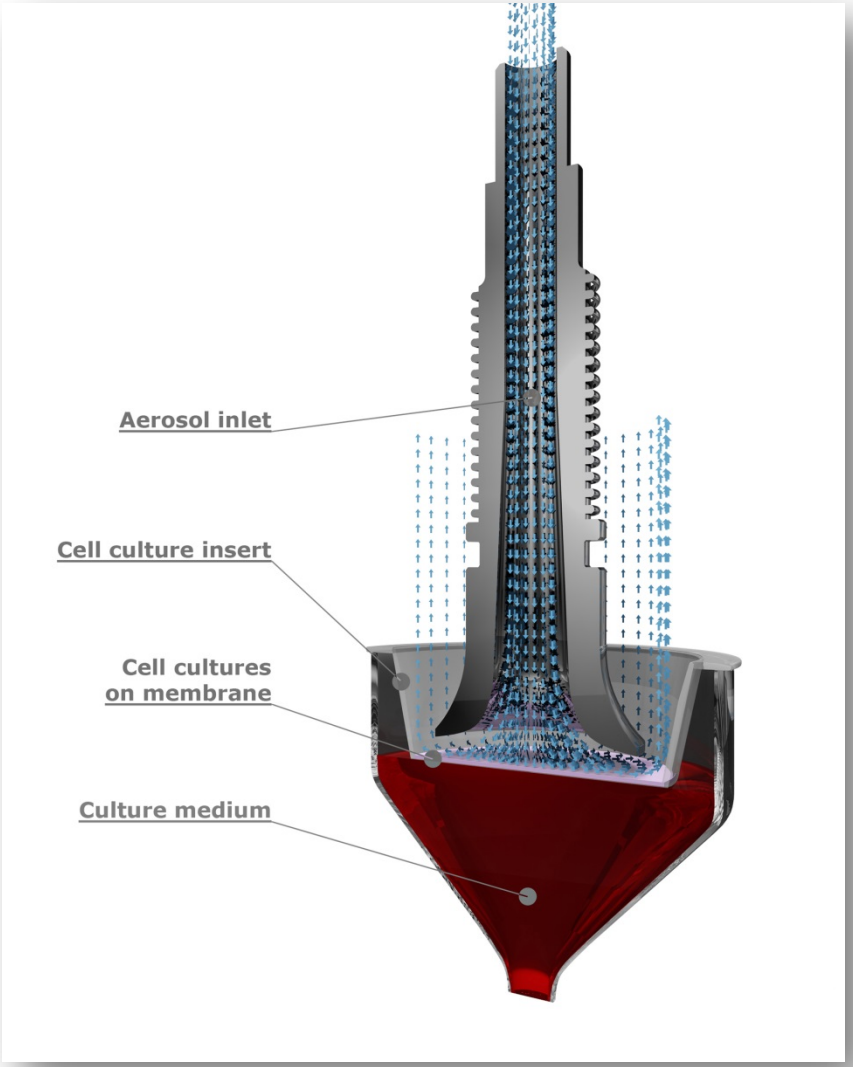
Air / Liquid Cultivation and Exposure in Exposure Module

A Direct and controlled exposure of test atmosphere to cells
B Cells on membrane
C Medium below cells

Air/Liquid Interface
High Sensitivity
Defined Dose

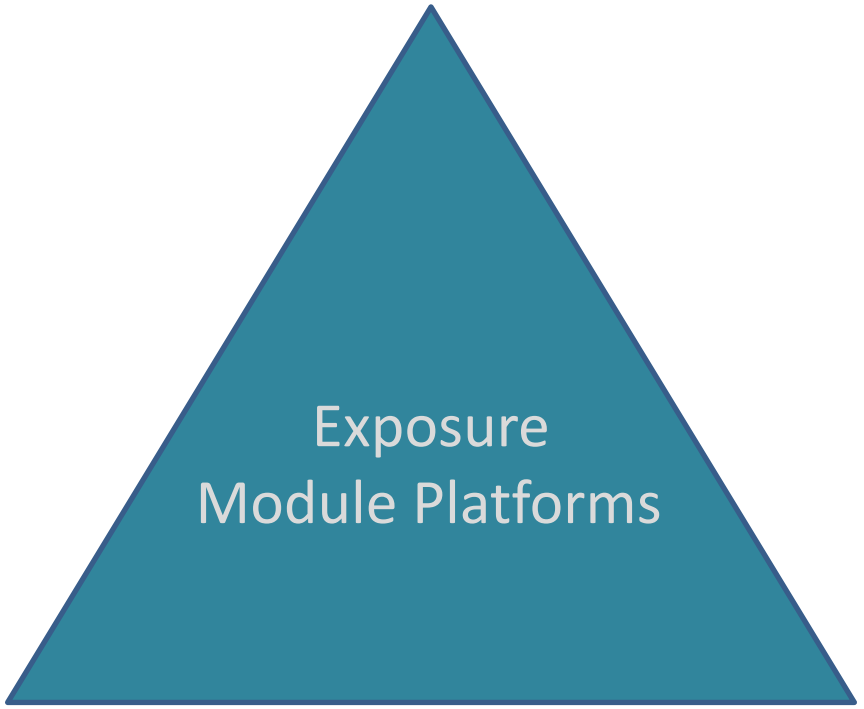
System Element: Exposure Module

Puff-by-Puff flow of diluted smoke to cell cultures



Choice of Exposure Module
VITROCELL® Exposure Module Platforms

Number of Doses/ Throughput
VC 96
VC 6/48
VC 24/48
VC 12/12
VC 12/6



Membrane Insert Size
6, 12, 24, 96 wells

Type of Assay
Mammalian cells
AMES
Suspension Cells

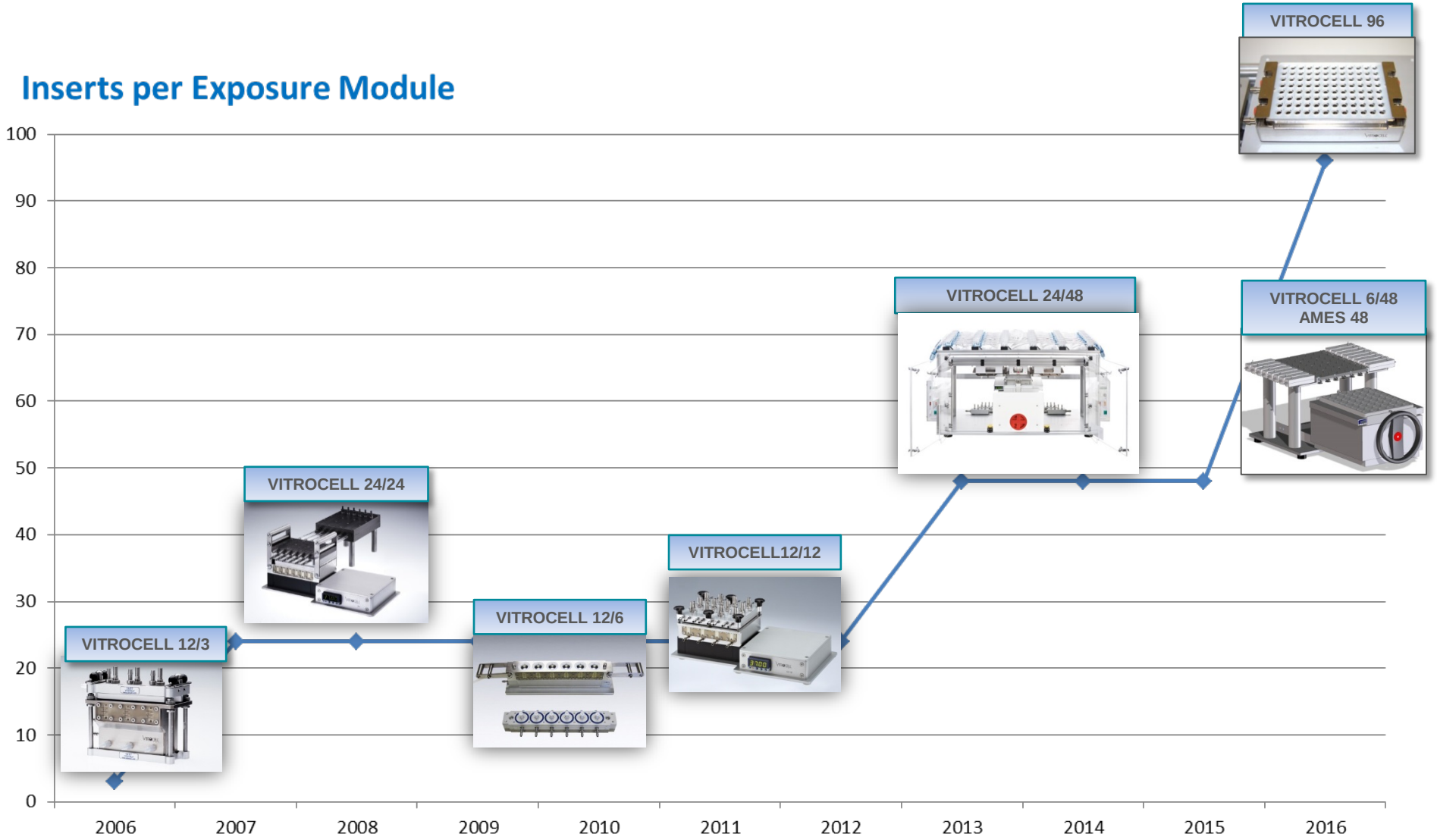
VITROCELL® Assay Guide

Category	Module type	VITROCELL 6 CF	VITROCELL 6/6 Cloud 6	VITROCELL 12 CF	VITROCELL 12/6	VITROCELL 12/6 CF	VITROCELL 12/12 Cloud 12	VITROCELL 24/24 Cloud 24	VITROCELL AMES	VITROCELL SC
	Number of inserts	3, 4 or 6	6	3 or 4	6	6	12	24 or 48	3 or 4	3 or 4
	Insert type (size)	6-well	6-well	12-well	12-well	12-well	12-well	24-well	35 mm Petri Dish	35 mm Petri Dish
	Culture Medium Supply	Continuous	Static	Continuous	Static	Continuous	Static	Static	--	--
Cytotoxicity	Number of viable cells	x	x	xx	xx	xx	xx	xx	–	–
	LDH release	xx	xx	xx	xx	xx	xx	x	–	–
	NRU uptake	x	x	xx	xx	xx	xx	xx	–	–
	MTT	x	x	xx	xx	xx	xx	xx	–	–
	XTT	x	x	xx	xx	xx	xx	xx	–	–
	MTS	x	x	xx	xx	xx	xx	xx	–	–
Proliferation	WST-1	x	x	xx	xx	xx	xx	xx	–	–
	Protein level	x	x	xx	xx	xx	xx	xx	–	–
Cellular Stress	ATP	xx	xx	x	x	x	x	x	–	–
	Cellular ATP/ADP ratio	xx	xx	x	x	x	x	x	–	–
	GSH	xx	xx	x	x	x	x	x	–	–
	GSSG	xx	xx	x	x	x	x	x	–	–
	GSSG/GSH	xx	xx	x	x	x	x	x	–	–
Oxidative Stress	Lipid peroxidation (MDA test)	xx	xx	x	x	x	x	x	–	–
Inflammation	Cytokines like IL8, IL6, IL12	x	x	xx	xx	xx	xx	x	–	–
Genotoxicity	Comet assay	x	x	xx	xx	xx	xx	–	–	–
	AMES/number of revertants	–	–	–	–	–	–	–	xx	–
"omic" technologies	ARN Sample for microarray	xx	xx	–	–	–	–	–	–	–
	ARN Sample for QRT PCR	xx	xx	–	–	–	–	–	–	–
Molecular Biology	Protein Sample for Western Blot	xx	xx	–	–	–	–	–	–	–
Assays for Suspension Cells		–	–	–	–	–	–	–	–	xx

Legend:
x = well suited
xx = particularly well suited

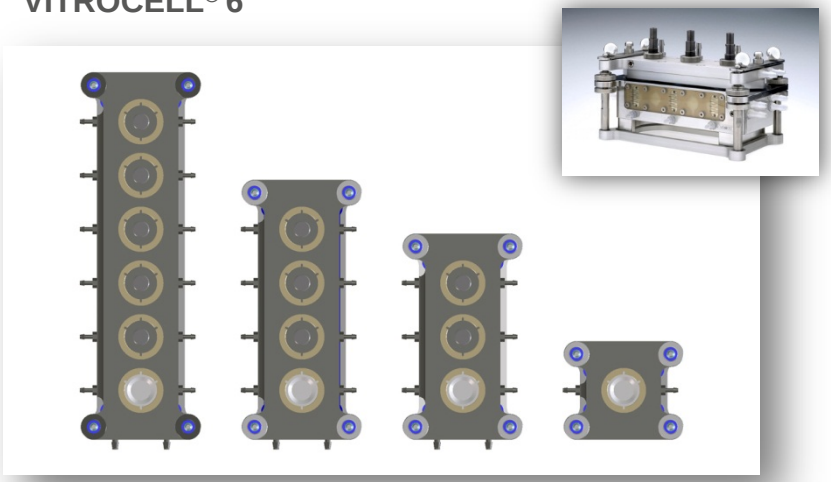
VITROCELL® Exposure Modules
Trend for higher throughput

Inserts per Exposure Module



VITROCELL® Universal Module Platforms

VITROCELL® 6



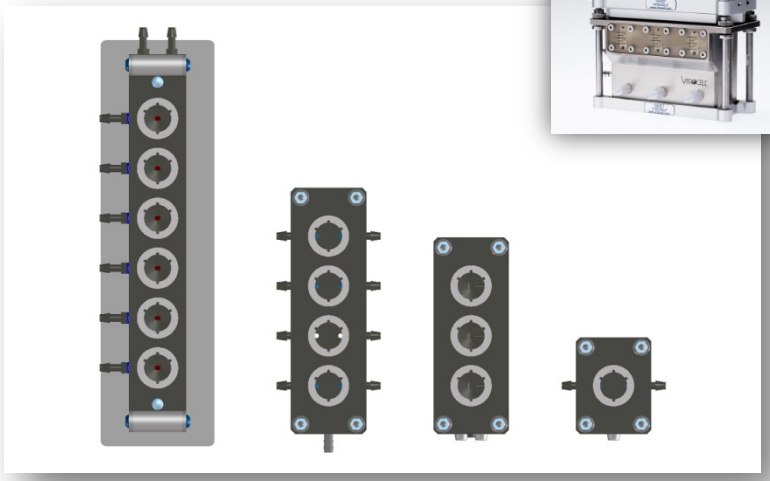
Insert Size

- 6-well
- 12-well
- 24-well
- Petri dishes AMES

Features

Medium reduction adaptors
Microbalance

VITROCELL® 12



- 12-well
- 24-well

Microbalance

Universal Modules for normal to medium throughput

Typical VC 1 and VITROCELL 12/6 Installation

Module system for 6 x 12- or 24-well sized cell culture inserts

- 1 dose @ 3 replicates
- 1 clean air control @ 3 replicates

VITROCELL® VC 1 for Electronic Cigarettes

MatTek CORPORATION

APPLICATION NOTE / VITROCELL

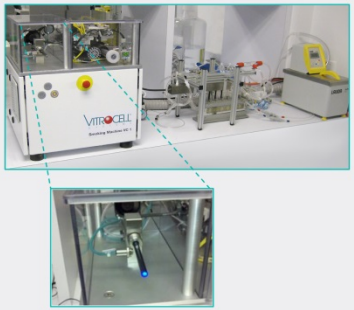
Using EpiAirway and EpiAlveolar with the VITROCELL® VC1 Smoking Machine and 12/6 CF Exposure Module

OBJECTIVE

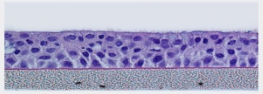
To evaluate the effects of whole tobacco smoke or electronic cigarette vapor using the EpiAirway and EpiAlveolar in vitro human airway models and the VITROCELL® exposure system.

ENDPOINTS

- Toxicity
- TEER
- Gene Expression
- Oxidative Stress
- Beating Cilia
- Mucus Secretion

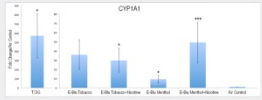


Typical setup of VITROCELL® exposure system utilized to expose EpiAirway or EpiAlveolar cultures to T-cig smoke or E-cig vapor. Inset shows E-blu E-cig in smoking chamber.

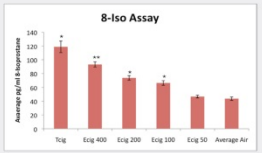


EpiAirway in vitro human tissue model. Stained histology 40X magnification

EpiAlveolar in vitro human tissue model. Stained histology 40X magnification



Quantitative PCR of CYP1A1 shows significant increases in expression after exposure of EpiAirway to TCIG smoke (48 puffs) and ECIG vapor (400 puffs).



8-Isoprostane in EpiAirway culture medium is significantly increased after both TCIG and ECIG exposure. 8-Isoprostane significantly increased after TCIG smoke exposure (48 puffs), or exposure to ECIG vapor (400, 200, 100 and 50 puffs).

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ARTICLE IN PRESS

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Development of an *in vitro* cytotoxicity model for aerosol exposure using 3D reconstructed human airway tissue; application for assessment of e-cigarette aerosol

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EpiAirway™
In vitro
Human airway

ABSTRACT

Development of physiologically relevant test methods to analyse potential irritant effects to the respiratory tract caused by e-cigarette aerosols is required. This paper reports the method development and optimisation of an acute *in vitro* MTT cytotoxicity assay using human 3D reconstructed airway tissues and an aerosol exposure system. The EpiAirway™ tissue is a highly differentiated *in vitro* human airway culture derived from primary human tracheal/bronchial epithelial cells grown at the air–liquid interface, which can be exposed to aerosols generated by the VITROCELL® smoking robot. Method development was supported by understanding the compatibility of these tissues within the VITROCELL® system, in terms of airflow (L/min), vacuum rate (mL/min) and exposure time. Dosimetry tools (QCM) were used to measure deposited mass, to confirm the provision of e-cigarette aerosol to the tissues. EpiAirway™ tissues were exposed to cigarette smoke and aerosol generated from two commercial e-cigarettes for up to 6 h. Cigarette smoke reduced cell viability in a time dependent manner to 12% at 6 h. E-cigarette aerosol showed no such decrease in cell viability and displayed similar results to that of the untreated air controls. Applicability of the EpiAirway™ model and exposure system was demonstrated, showing little cytotoxicity from e-cigarette aerosol and different aerosol formulations when compared directly with reference cigarette smoke, over the same exposure time.

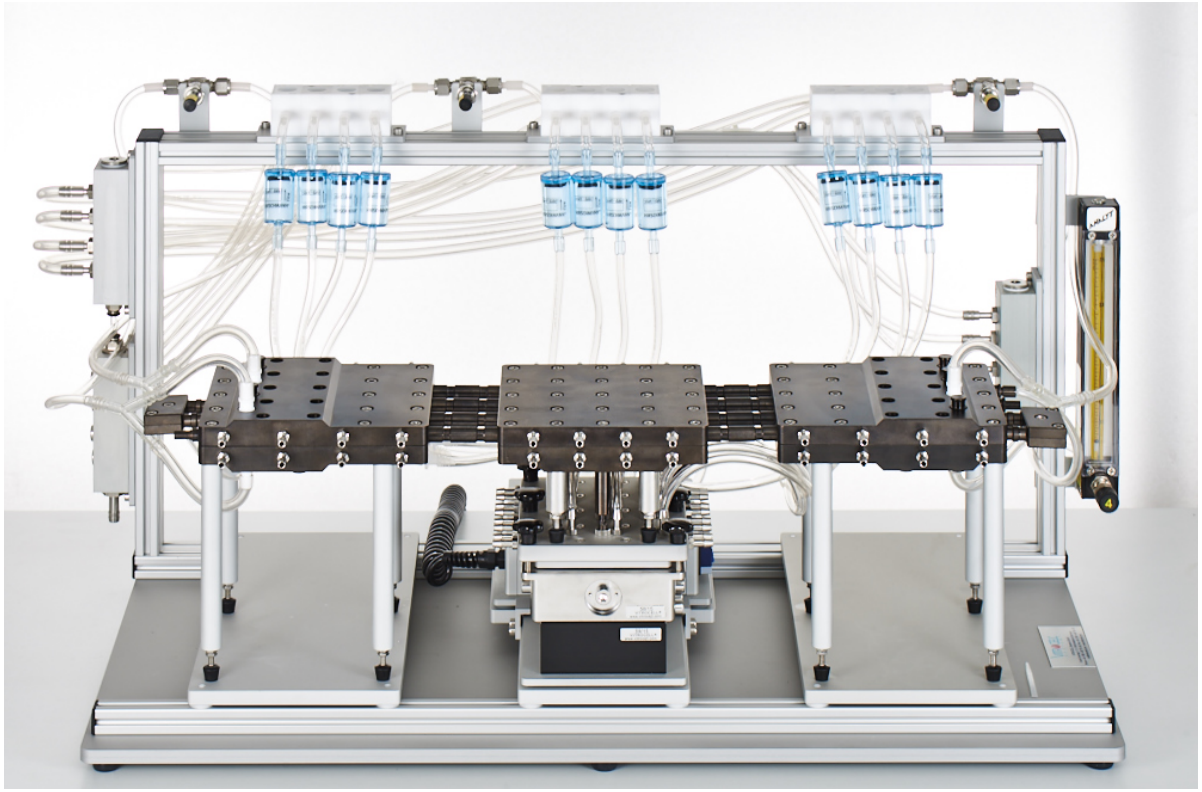
1. Introduction

E-cigarettes[1] are increasing in popularity throughout the world. Whilst the devices themselves are subject to some regulation, e.g. CE marking, there are no standard regulations relating to characterbeen done. Desk-based risk assessment of the ingredients contained within e-liquids has highlighted a specific requirement to understand the potential for irritant effects to the respiratory tract caused by e-cigarette aerosols.

A number of *in vitro* tests, largely been based on cytotoxicity

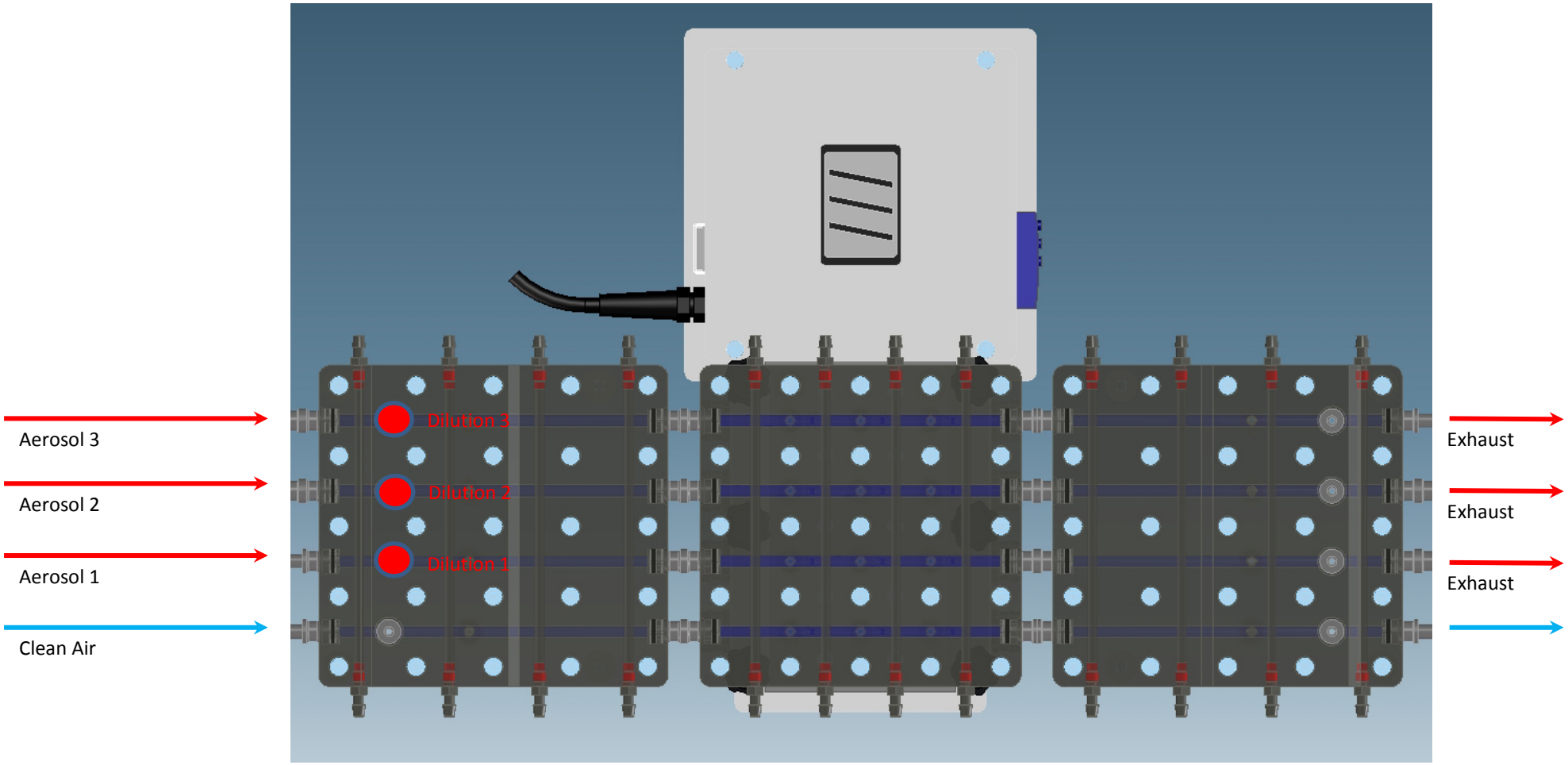
VITROCELL® 12/12
Module system for 12 x 12- and 24-well sized cell culture inserts

VITROCELL® 12/12 Quick-Connect Station

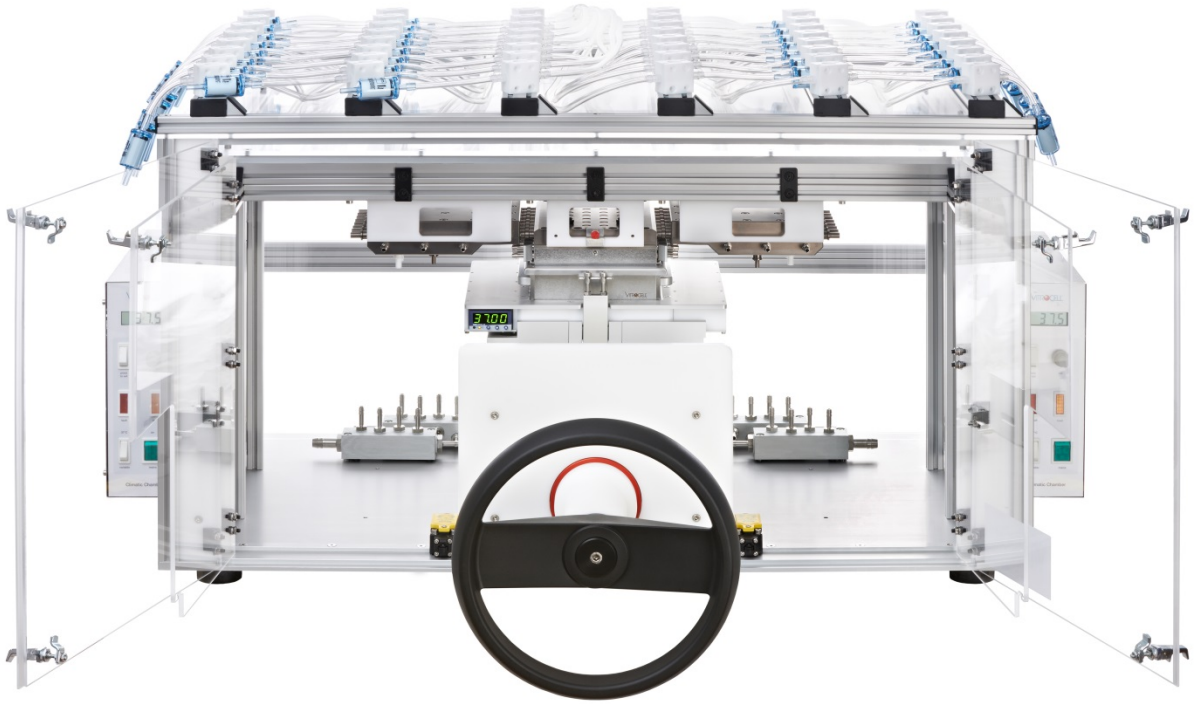


- 3 doses @ 3 replicates
- 1 clean air control @ 3 replicates
- Integrated dynamic dilution systems

VITROCELL® 12/12
Dilution System – 3 aerosol entries / 1 clean air

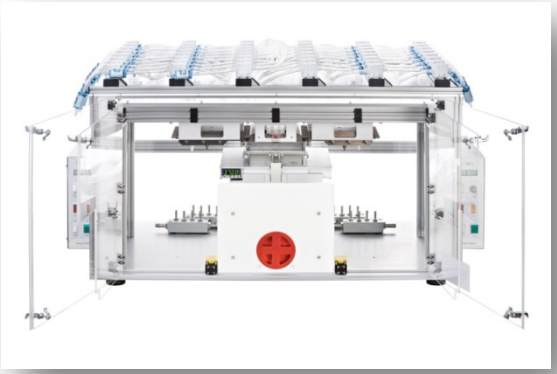


VITROCELL® 24/48
Module system for 48 x 24-well sized cell culture inserts



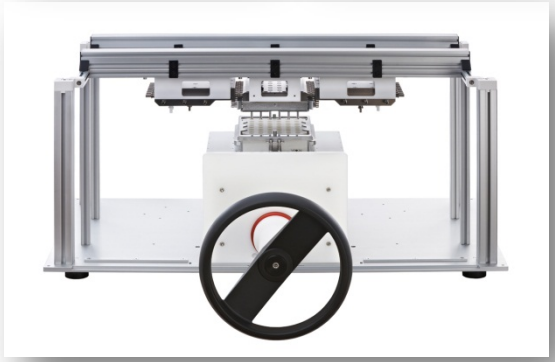
7 doses @ 6 replicates
1 clean air control @ 6 replicates
Integrated dynamic dilution systems

VITROCELL® 24/48
Module system for 48 x 24 well sized cell culture inserts



- 7 doses @ 6 replicates
- 1 clean air control @ 6 replicates
- Integrated dynamic dilution systems

- Exposure Top with VITROCELL® 24 /24 technology
- Base module with 8 rows @ 6 replicates

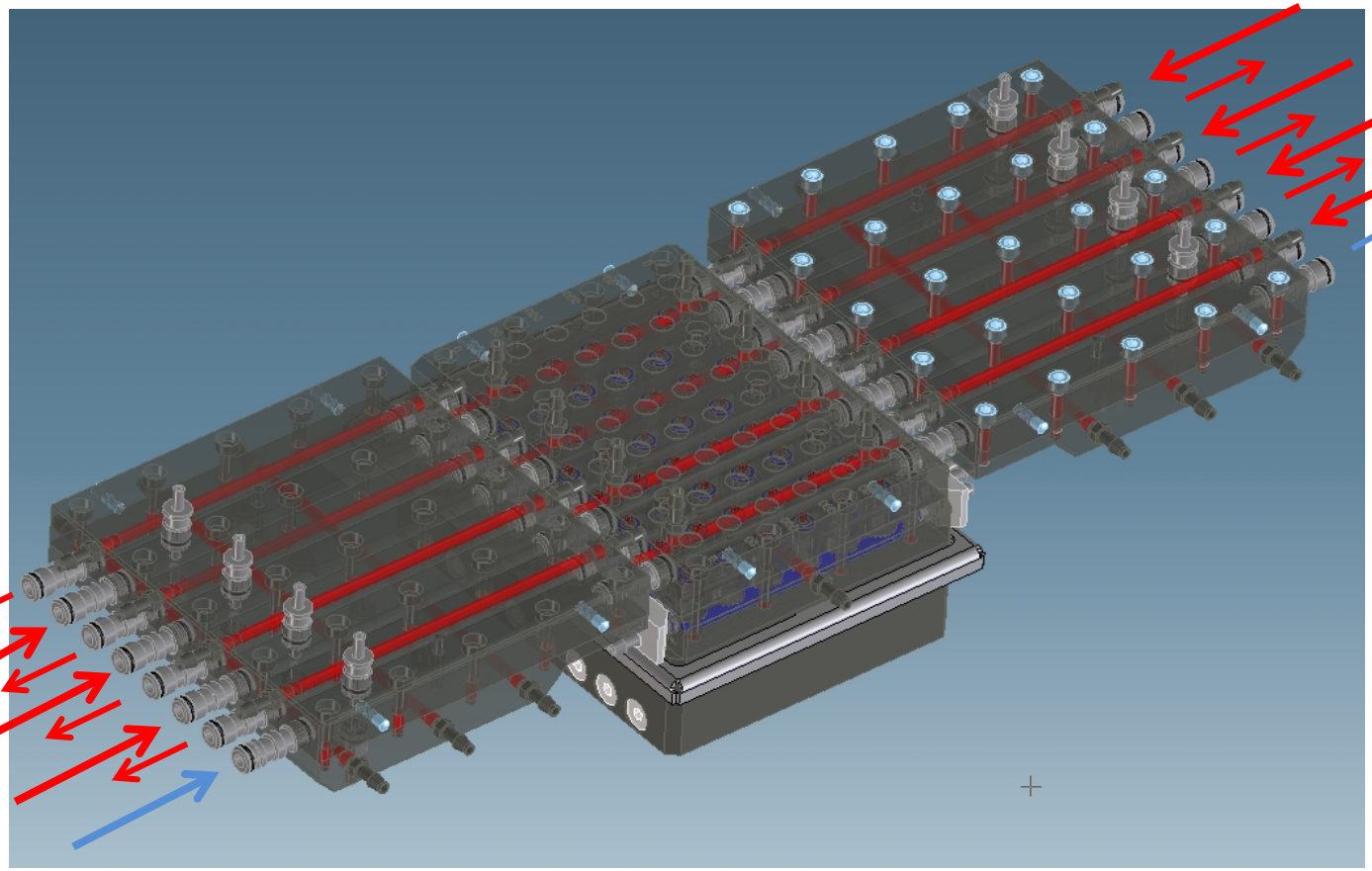


- Rack with unique locking device

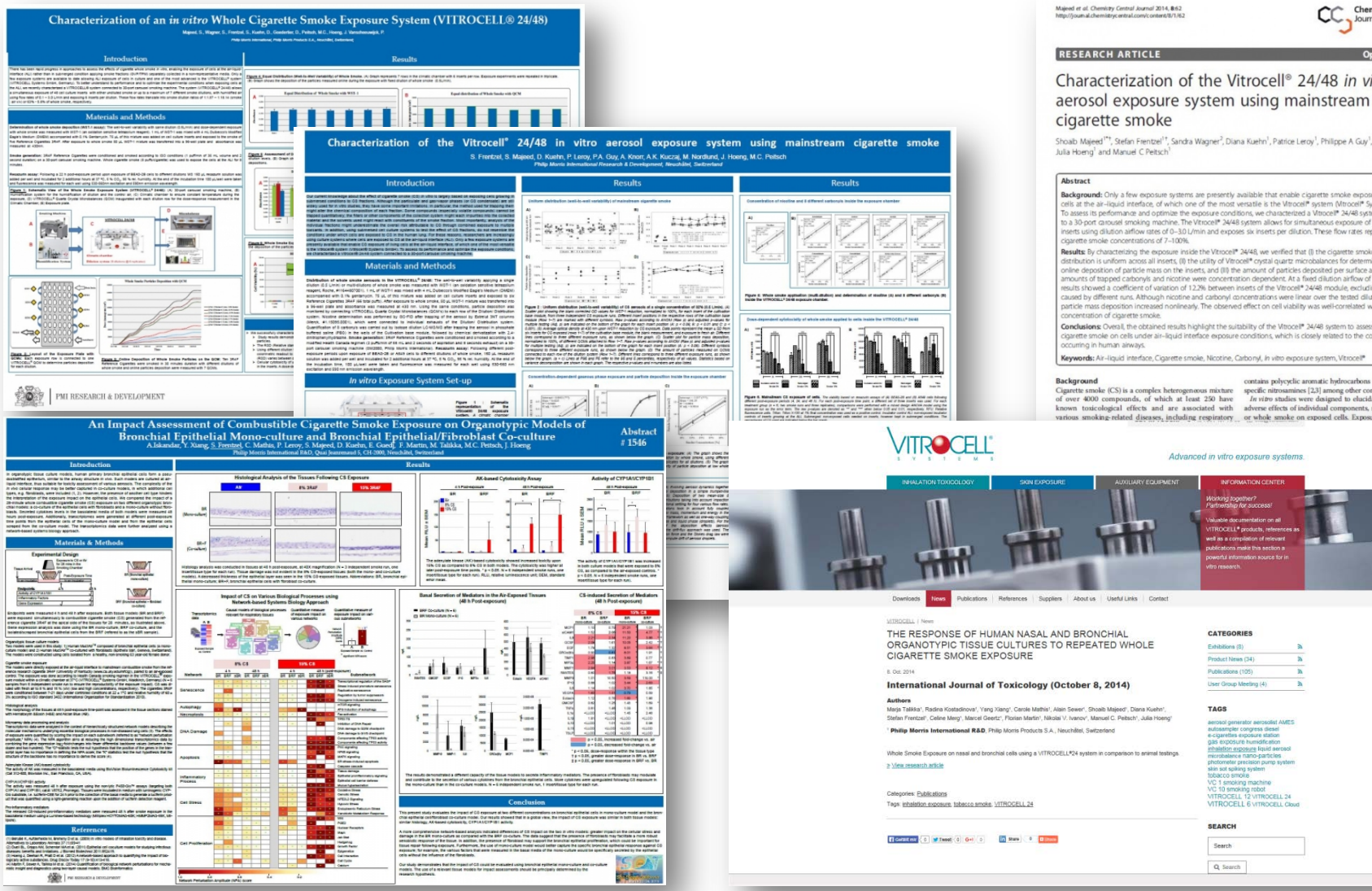
Module system for higher throughput

VITROCELL® 24/48
Dilution System – 7 aerosol entries / 1 clean air

- 7 doses @ 6 replicates
- 1 clean air control @ 6 replicates
- Integrated dynamic dilution systems

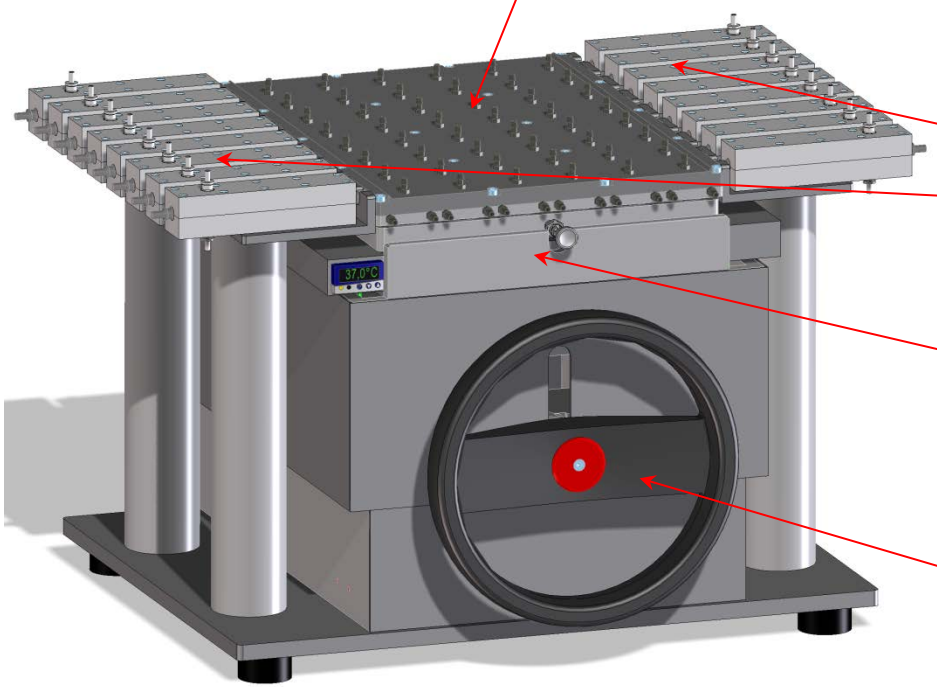


VITROCELL® 24/48 Publications



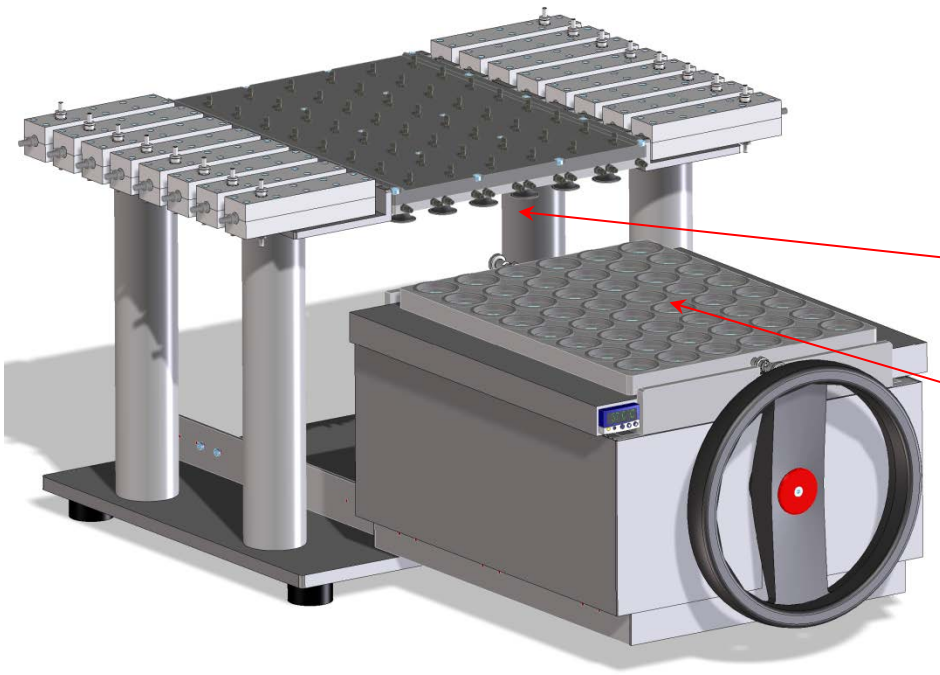
VITROCELL® 6/48 and AMES 48

Module for 48 x 6 well sized cell culture inserts / 35 mm Petri dishes



VITROCELL® 6/48 and AMES 48

Module for 48 x 6 well sized cell culture inserts / 35 mm Petri dishes

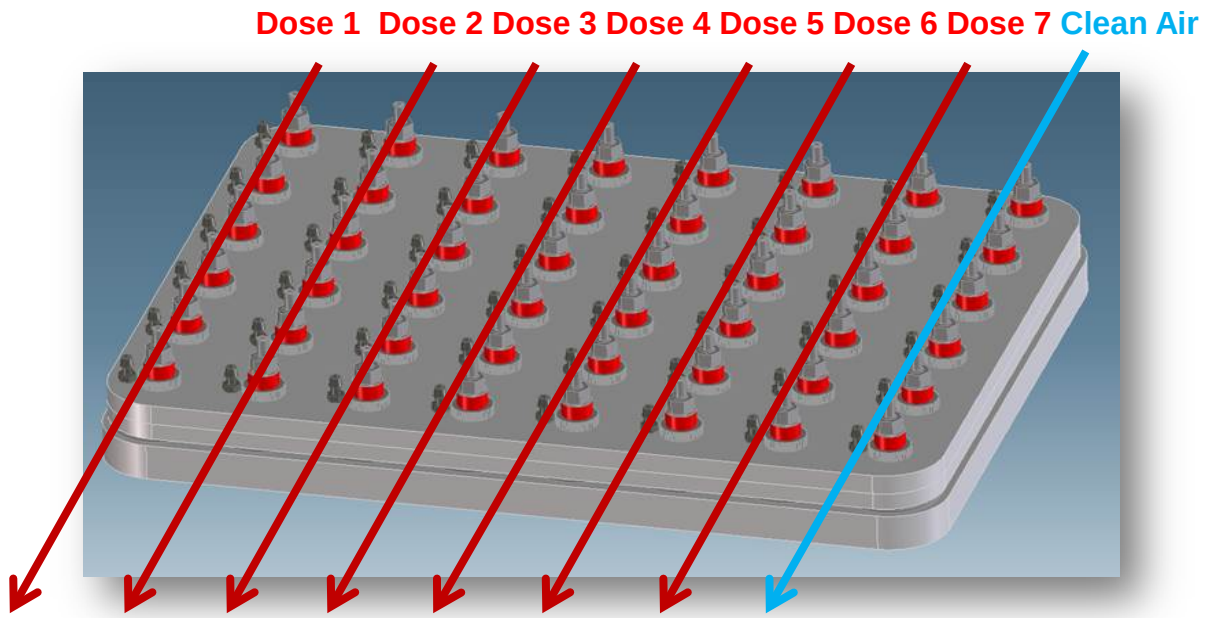


Aerosol Inlets / Trumpets

Exposure Base Module

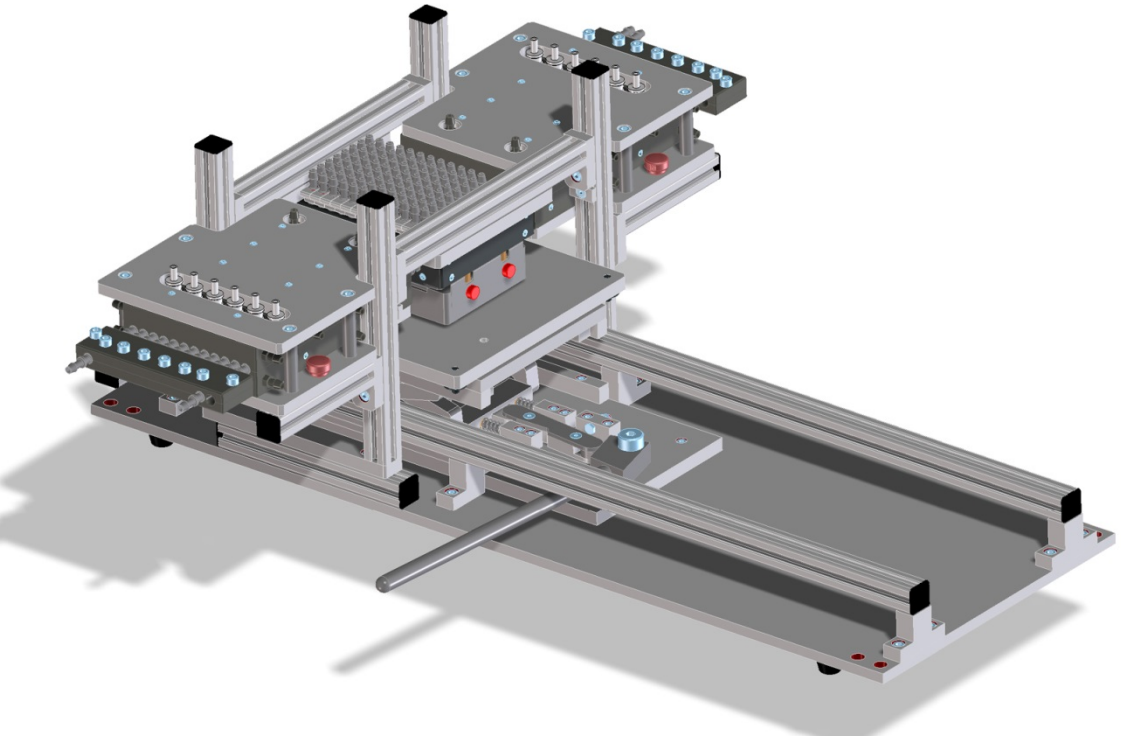
VITROCELL® 6/48 and AMES 48
Dilution System – 7 aerosol entries / 1 clean air

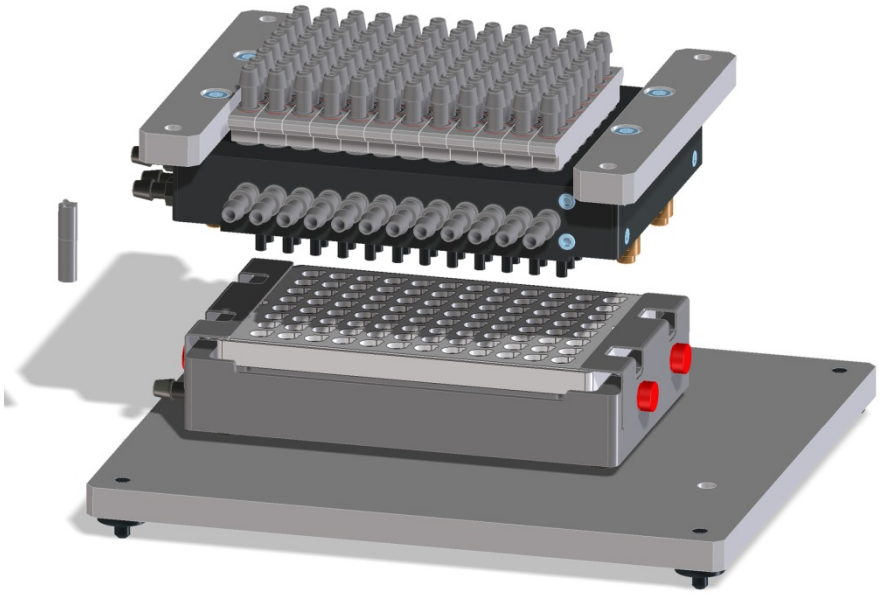
- Increase of capacitiy, in a compact design
- 7 Doses @ 6 replicates
- 1 clean air control @ 6 replicates
- Flexible design, AMES and 6-well compatibility



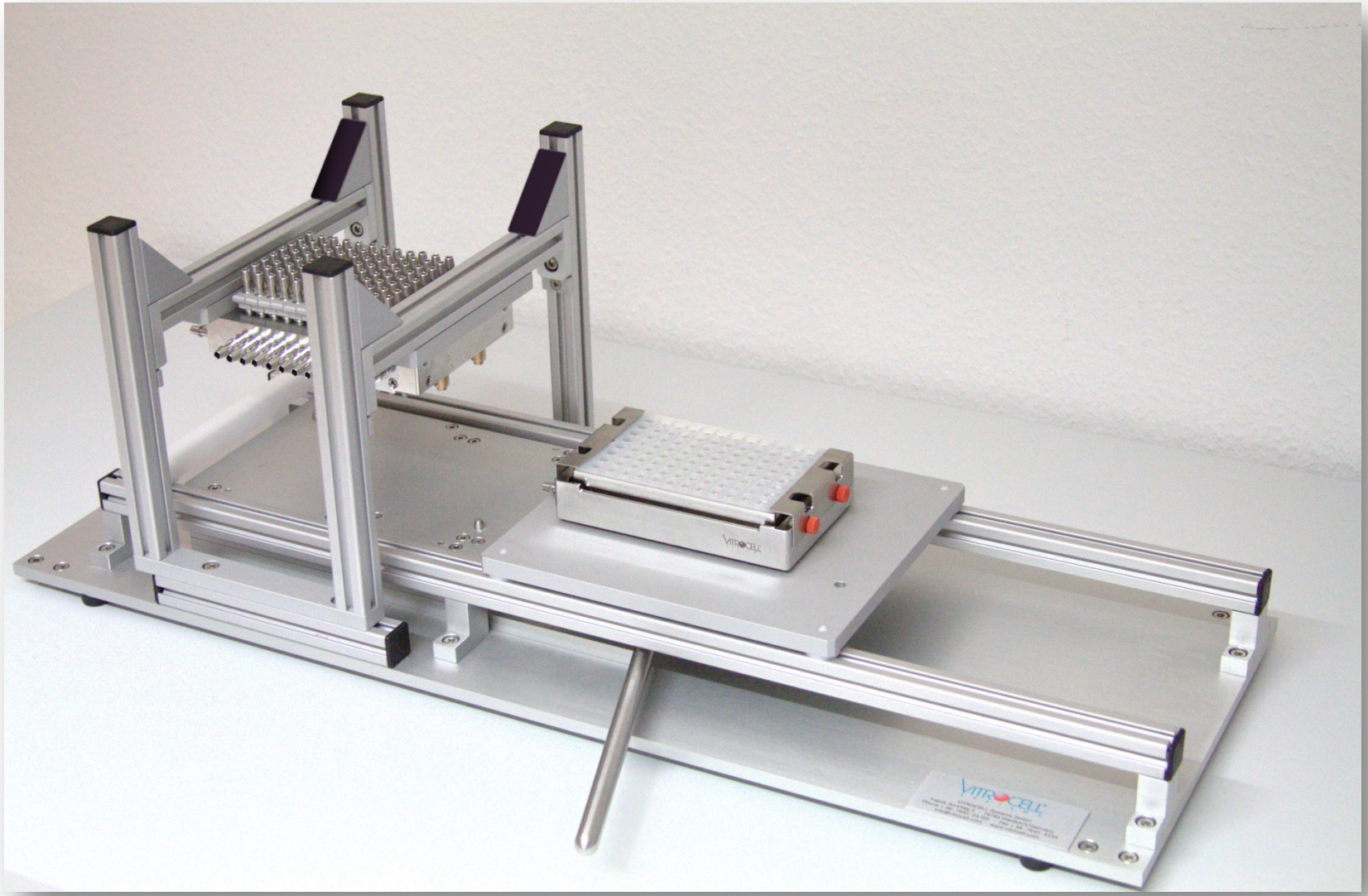
VITROCELL® 96
Module for 96-well sized cell culture insert plates

- 11 doses @ 8 replicates
- 1 clean air control @ 8 replicates
- Integrated dynamic dilution system

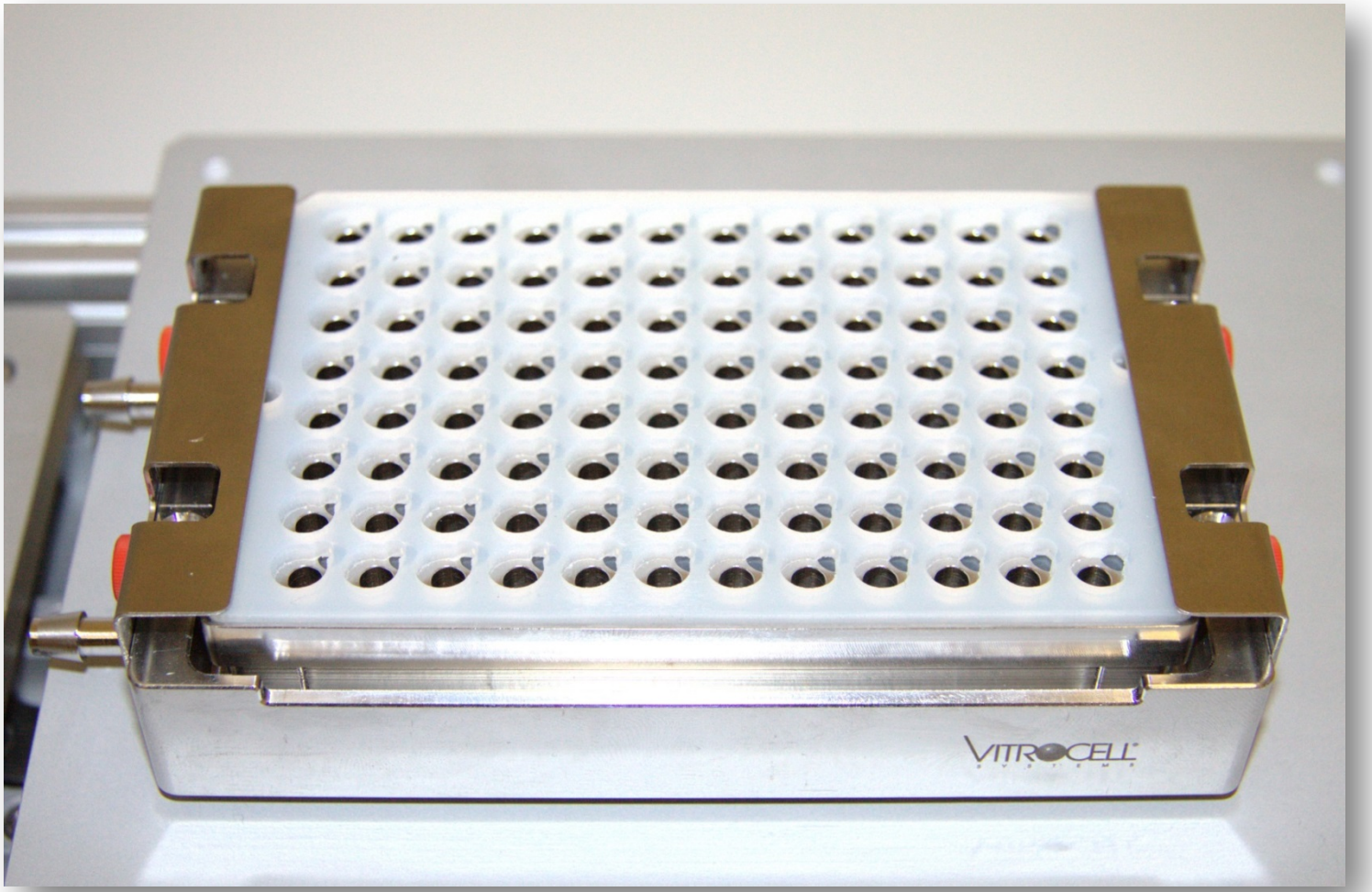




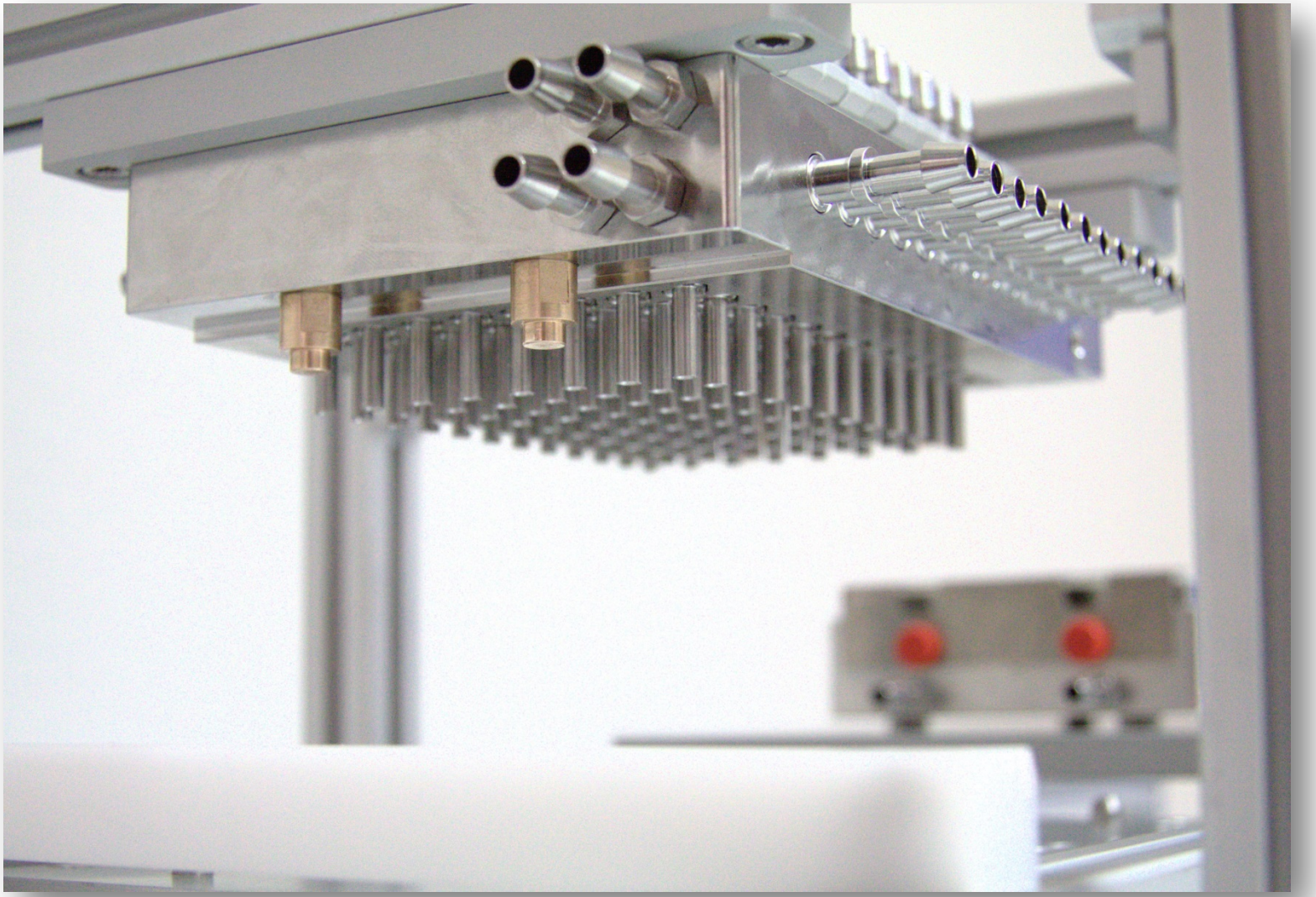
VC 96 Rack System



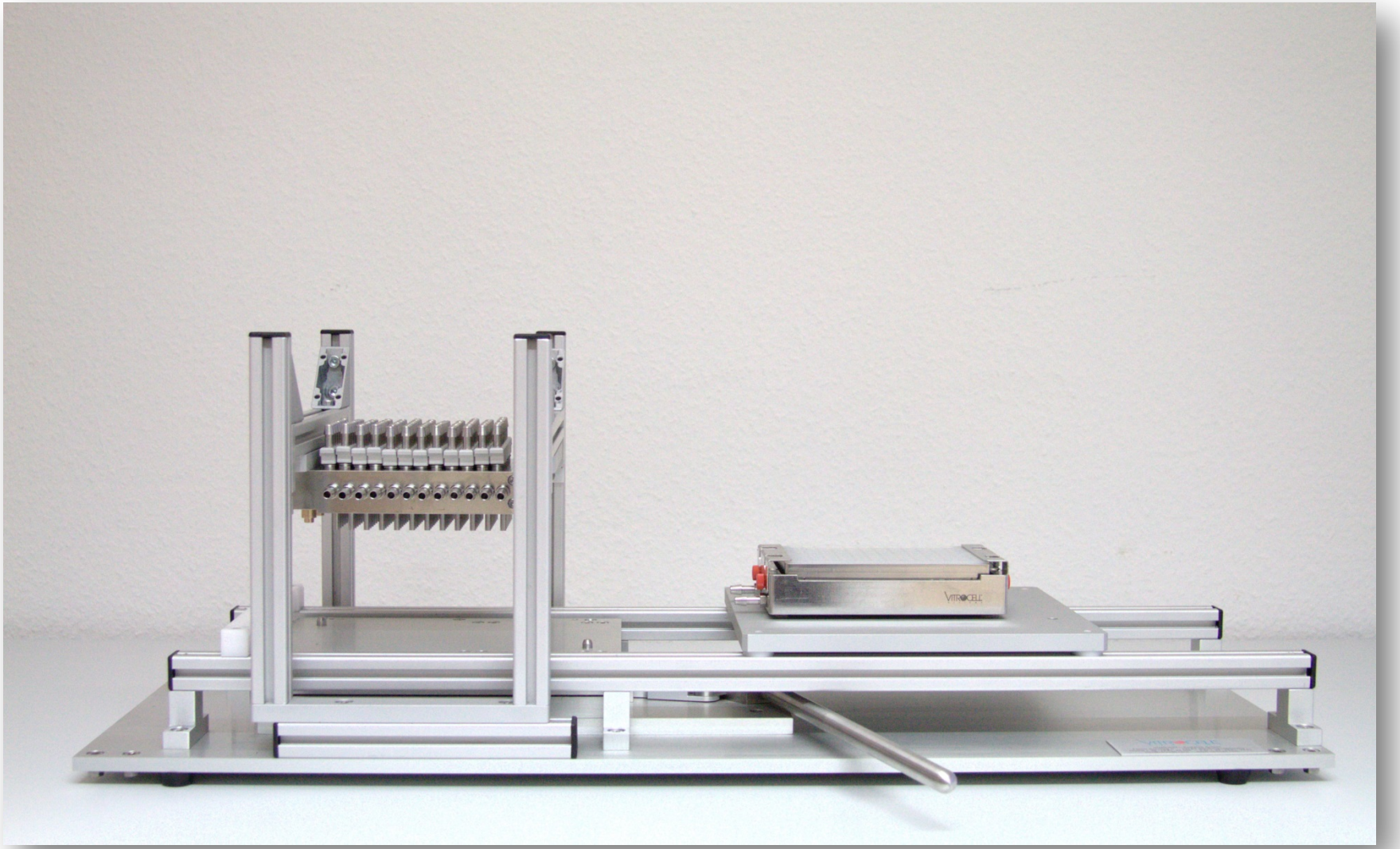
VITROCELL® 96
Base Module



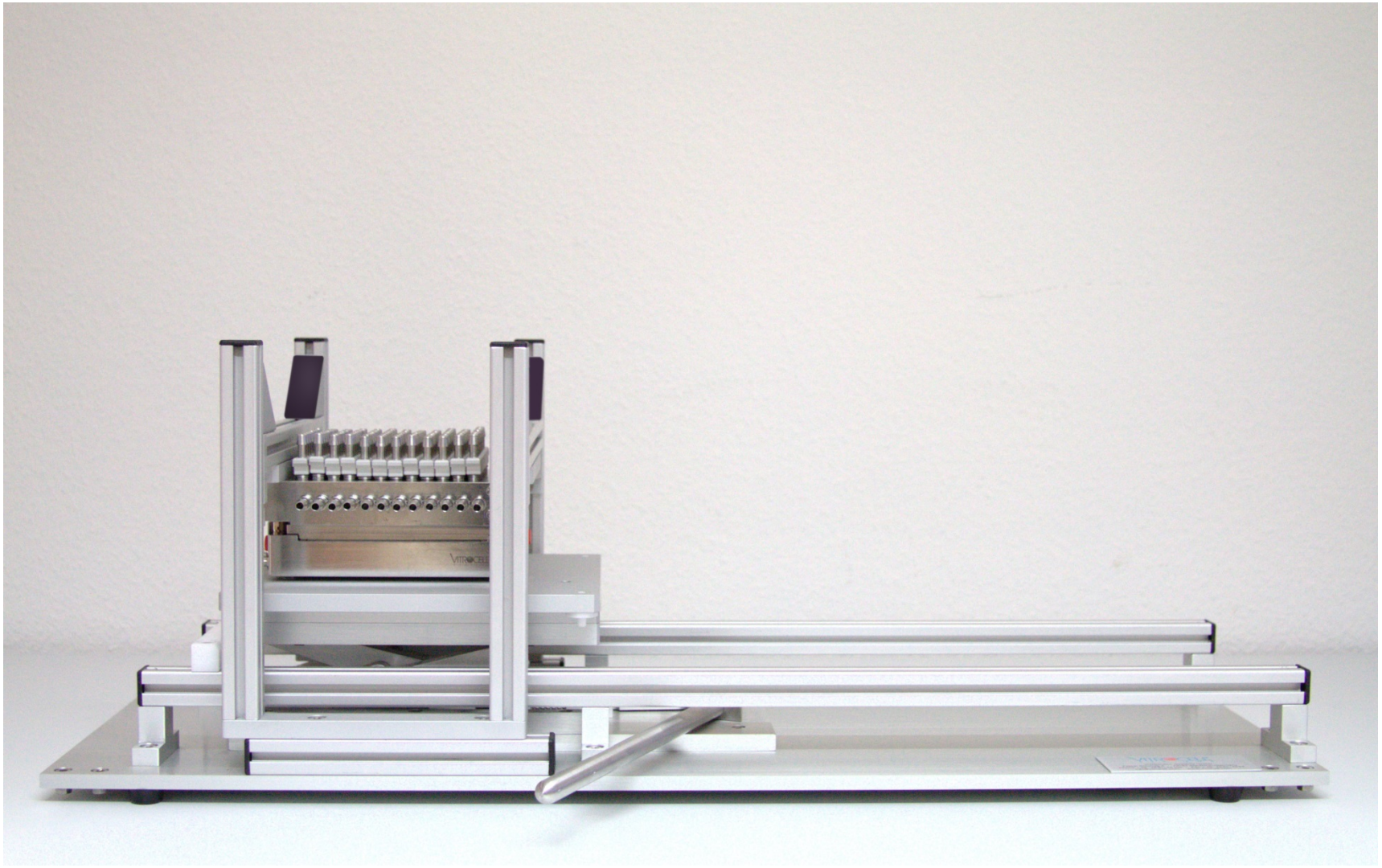
VITROCELL® 96
Exposure Top



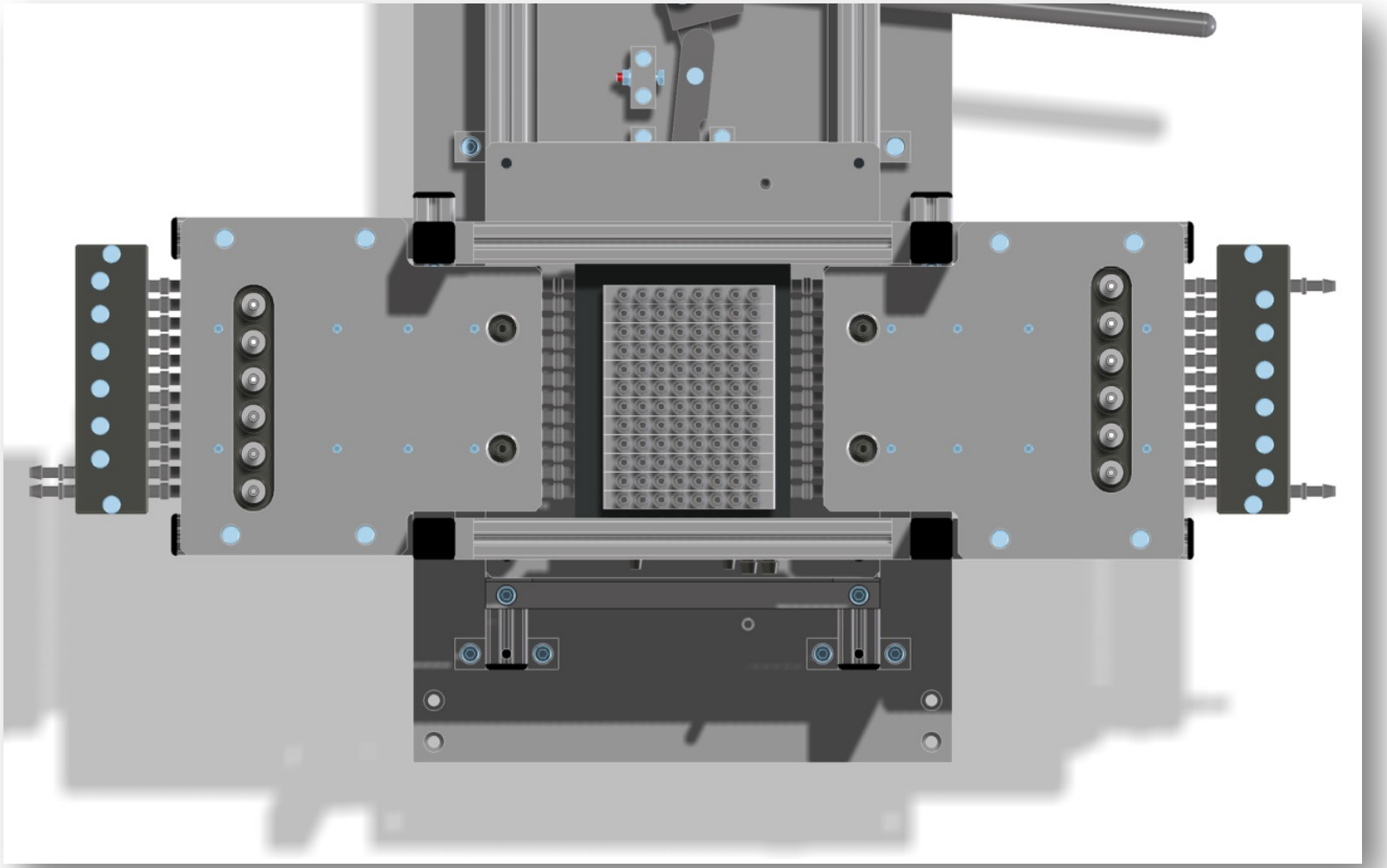
VITROCELL® 96
Locking Device



VITROCELL® 96
Locking Device

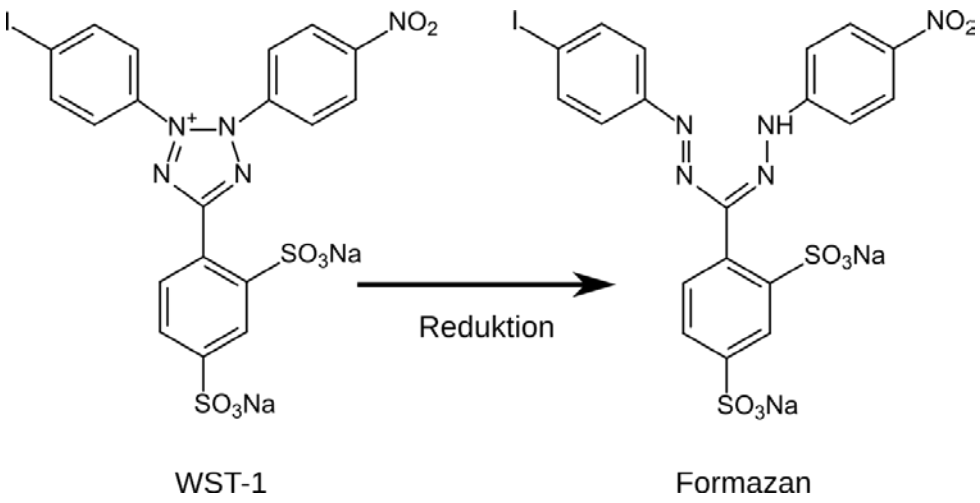


VITROCELL® 96
Dilution System – 11 aerosol doses / 1 clean air

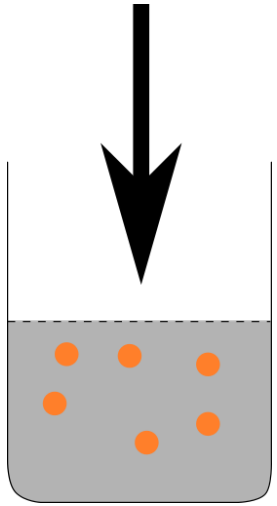


Test of equal distribution using tobacco smoke

WST-1



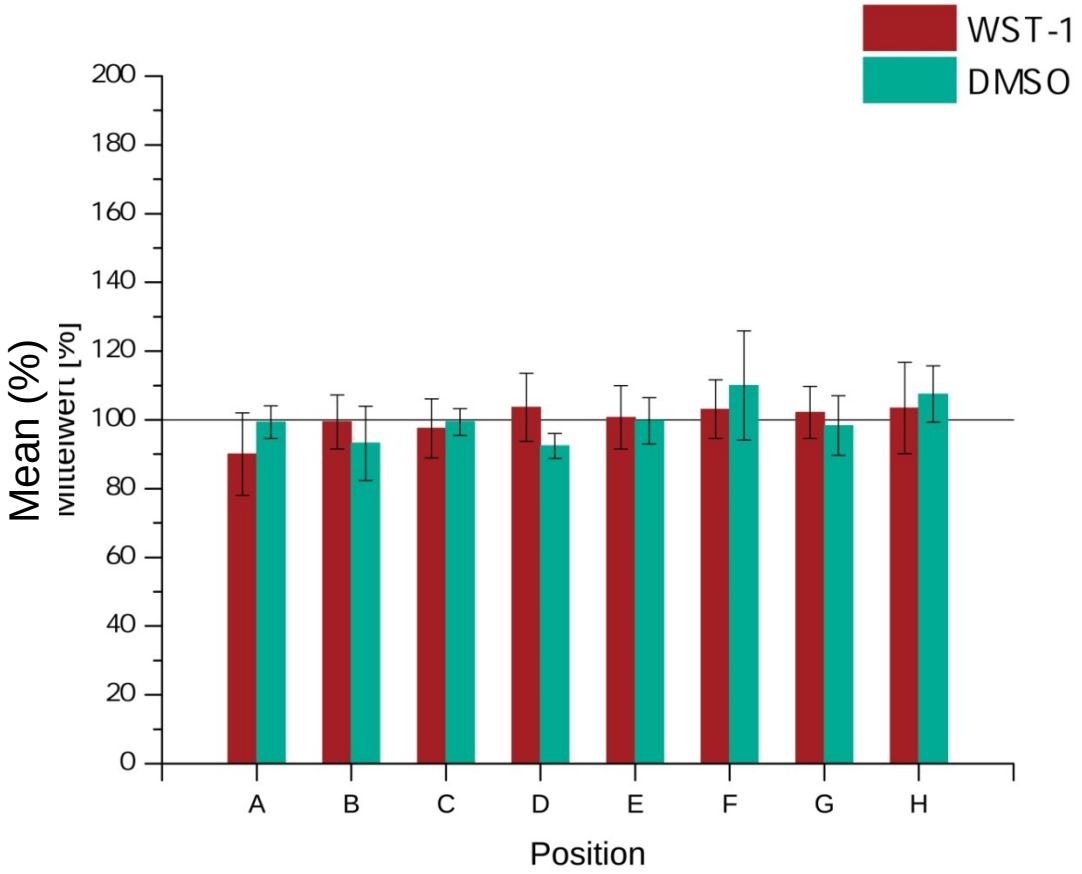
DMSO



- Reduction by cigarette smoke
- Colour change
- Absorption measurement at 450 nm

- Depostion and dissolution of particles

Test of equal distribution using tobacco smoke



WST-1

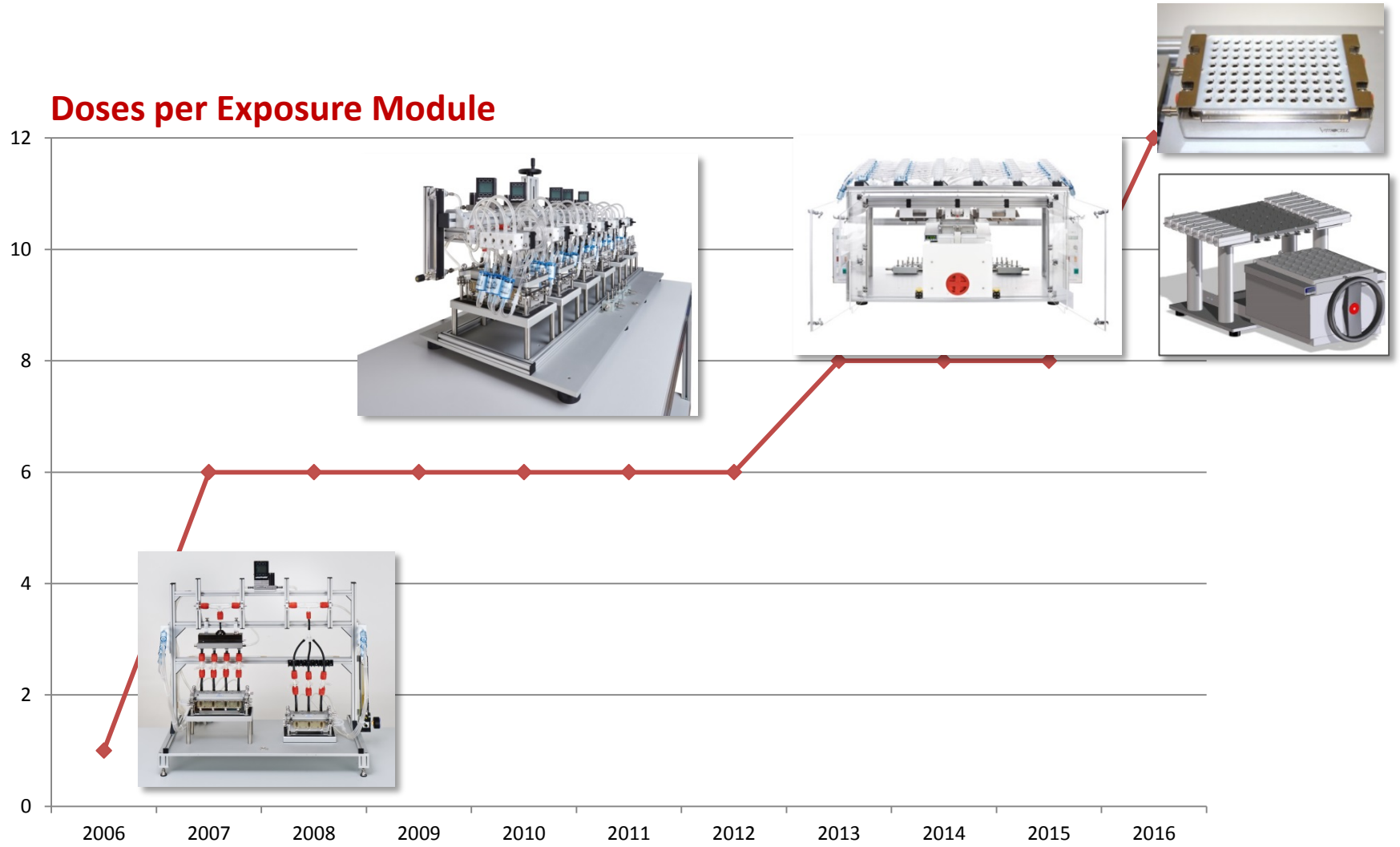
Dilution rate 1l/min
Vacuum flow 1.2 ml/min
N=5
5 Cigarettes, 8 puffs, ISO

DMSO

Dilution rate 1l/min
Vacuum flow 0.5-1.0-2.0 ml/min
N=3
5 Cigarettes, 8 puffs, ISO

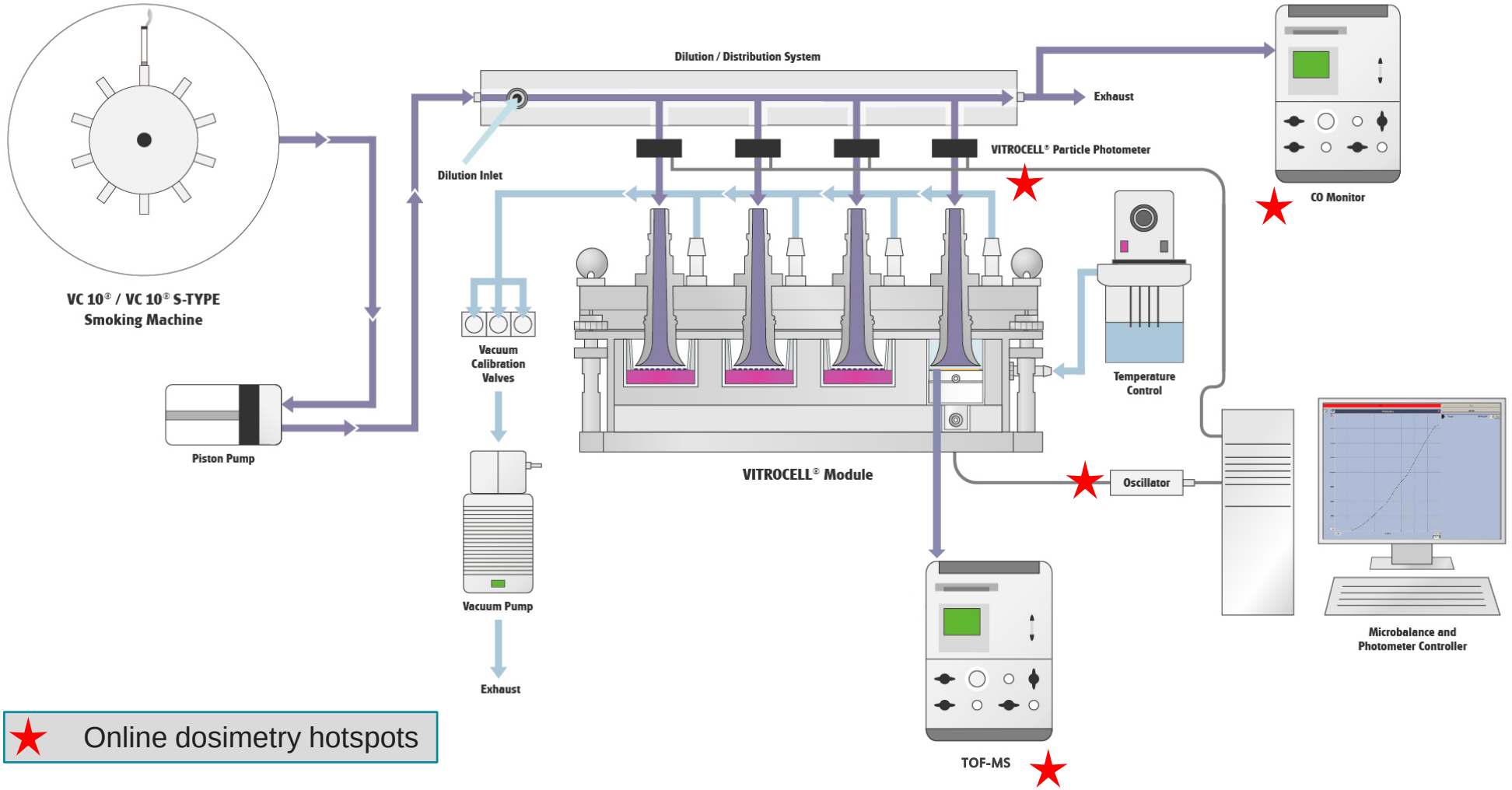
VITROCELL® Installations

Trend for higher throughput at multiple doses

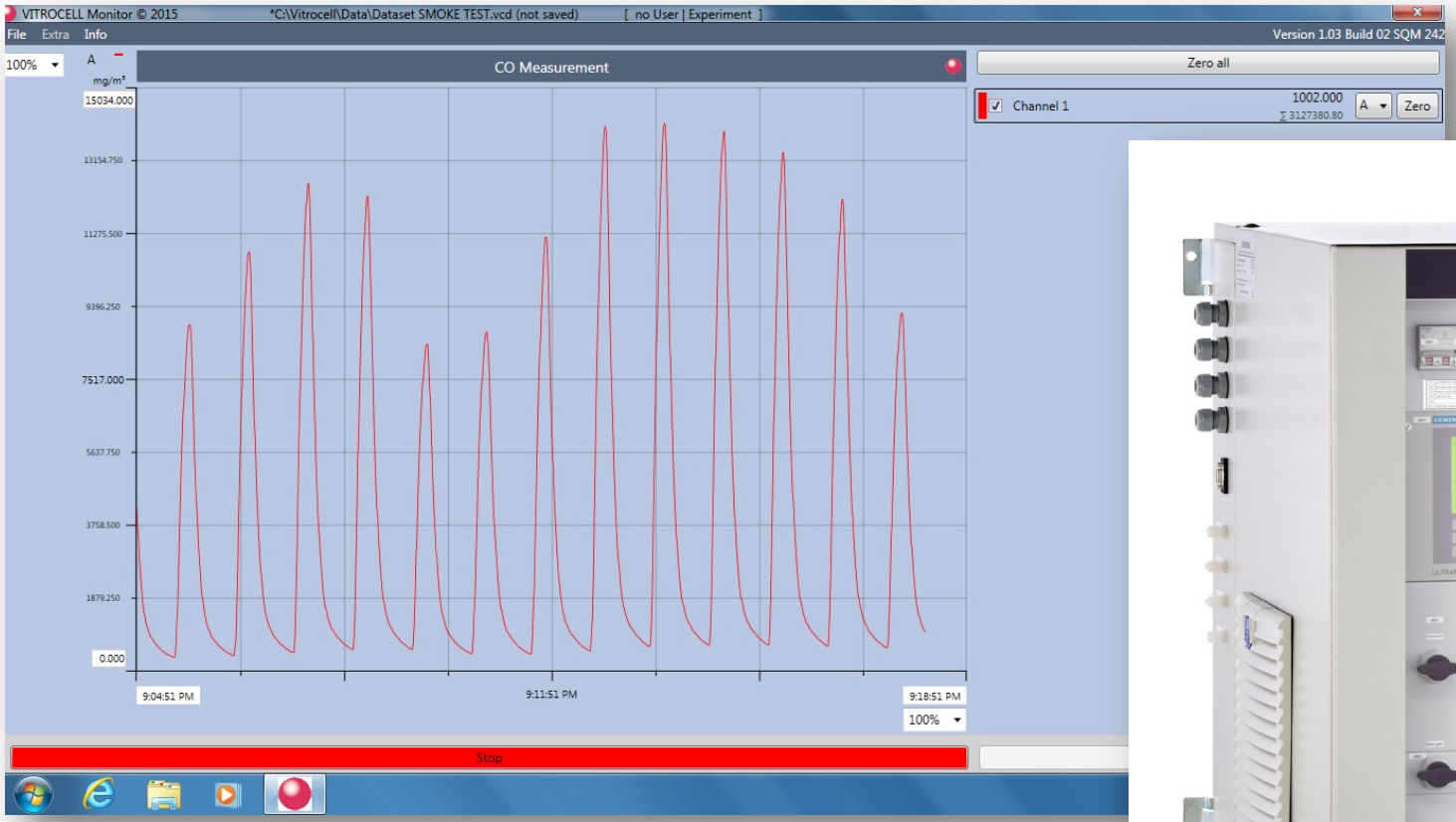


Typical Installation for Suspension Cells

System Element: Online Dosimetry Tools

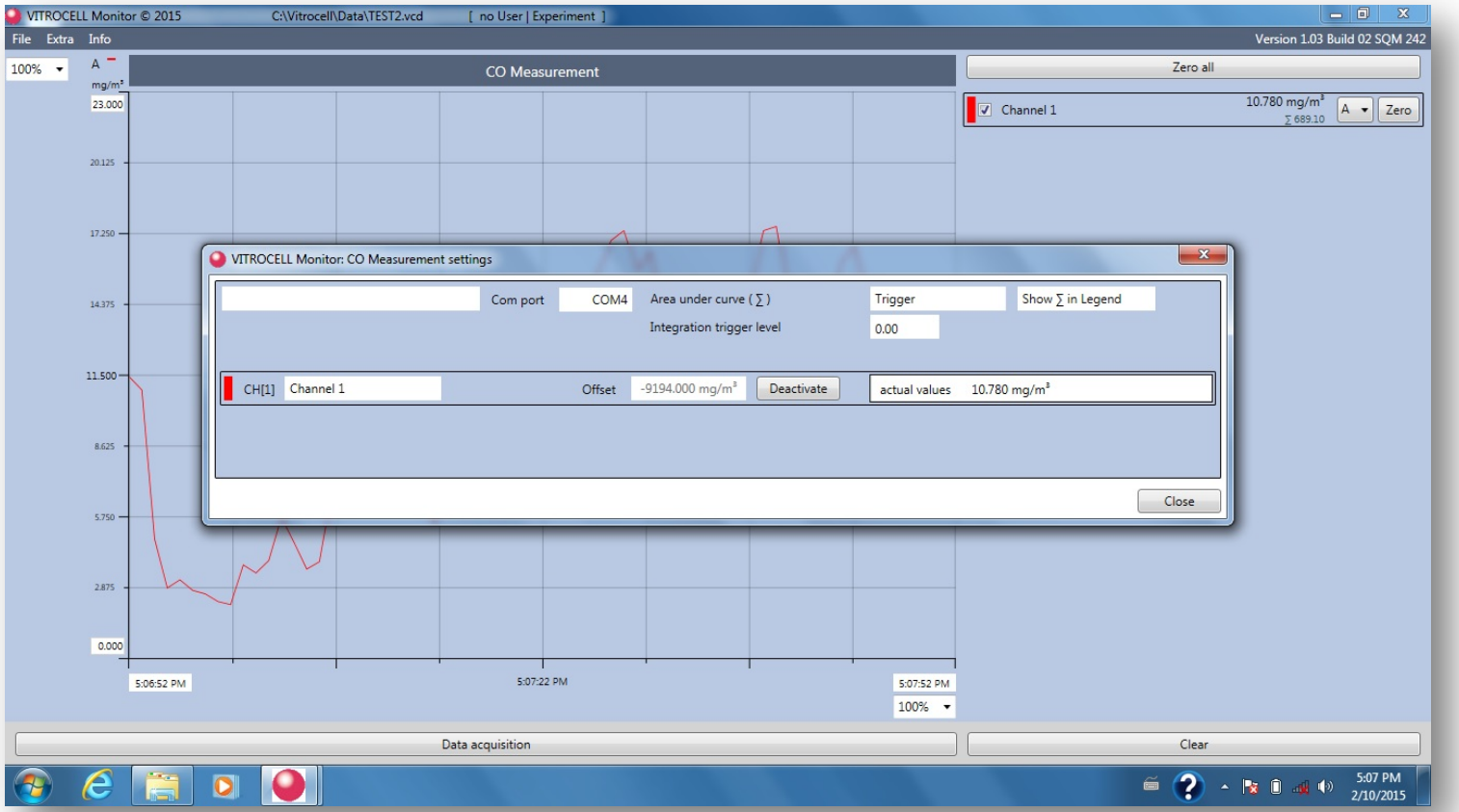


VITROCELL® CO Online Monitoring Software



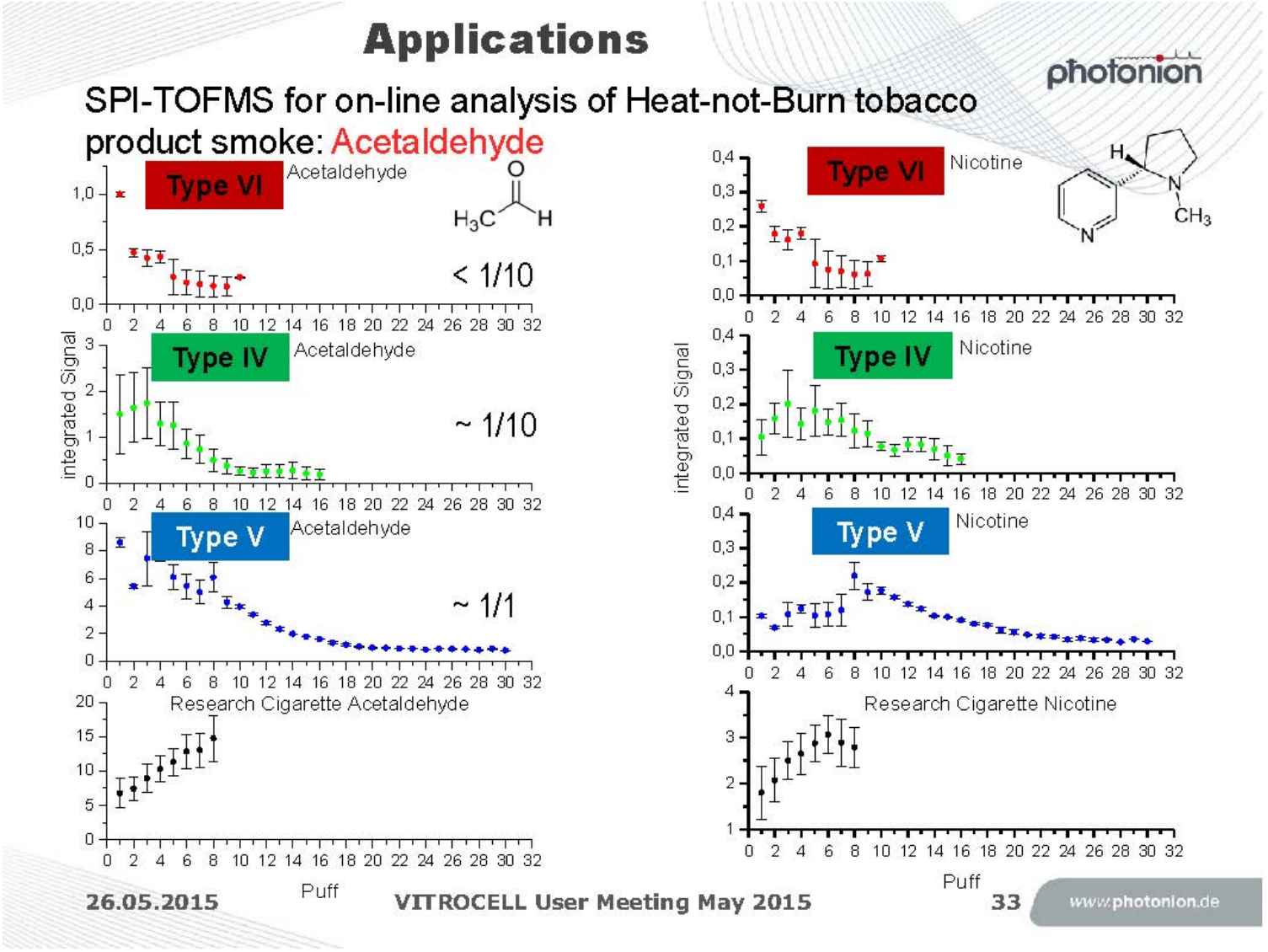
Online monitoring of each puff

VITROCELL® CO Online Monitoring Software

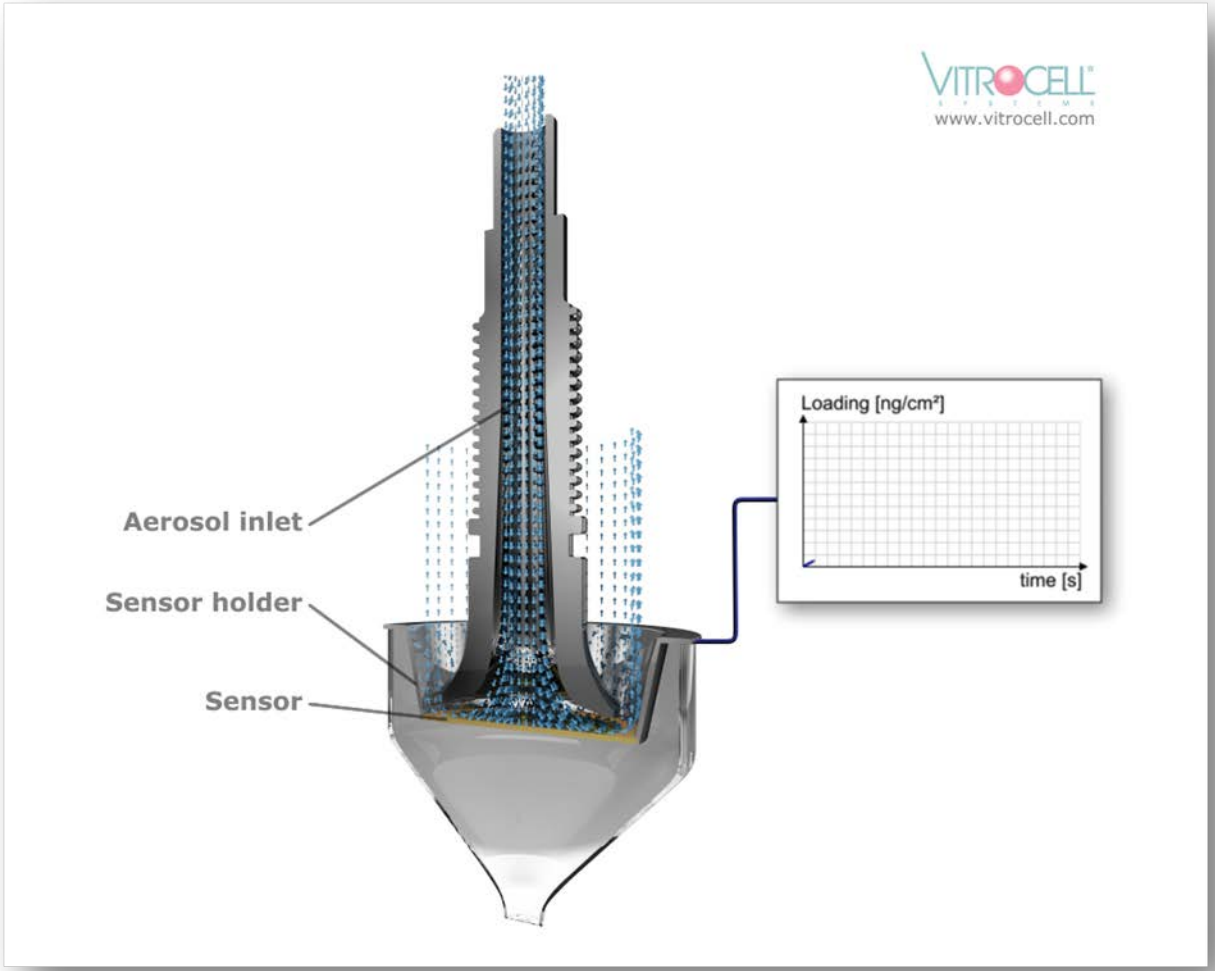


Area under curve function (same as photometer software)

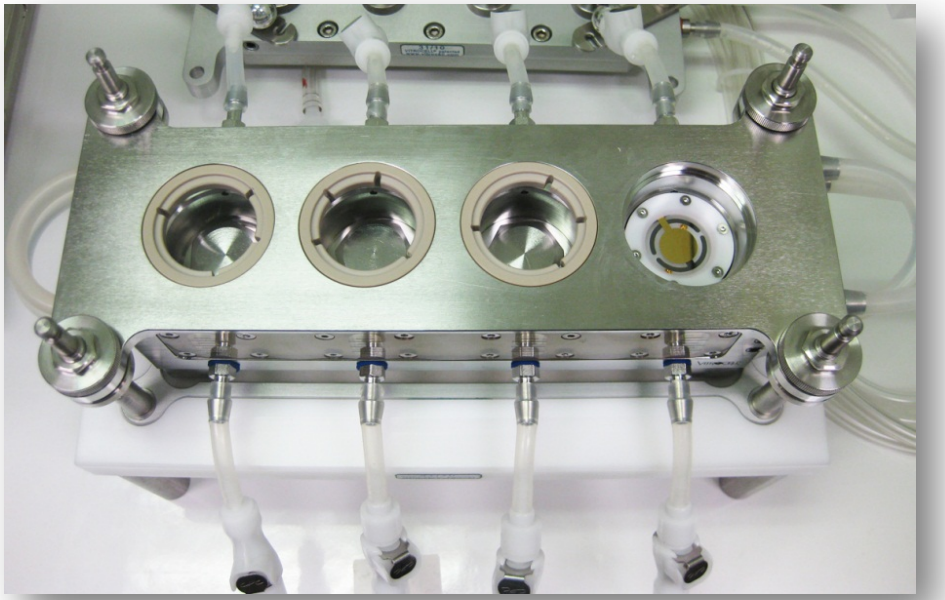
Online TOF-MS

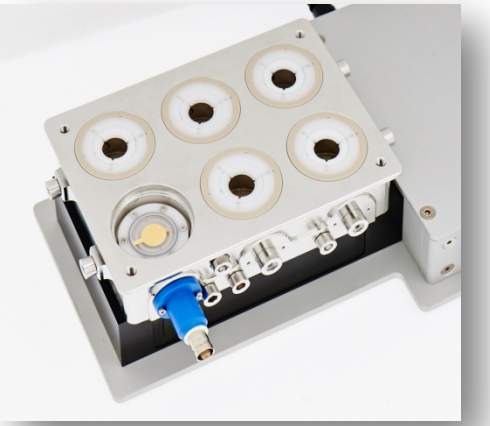


Dose Monitoring with Microbalance Technology

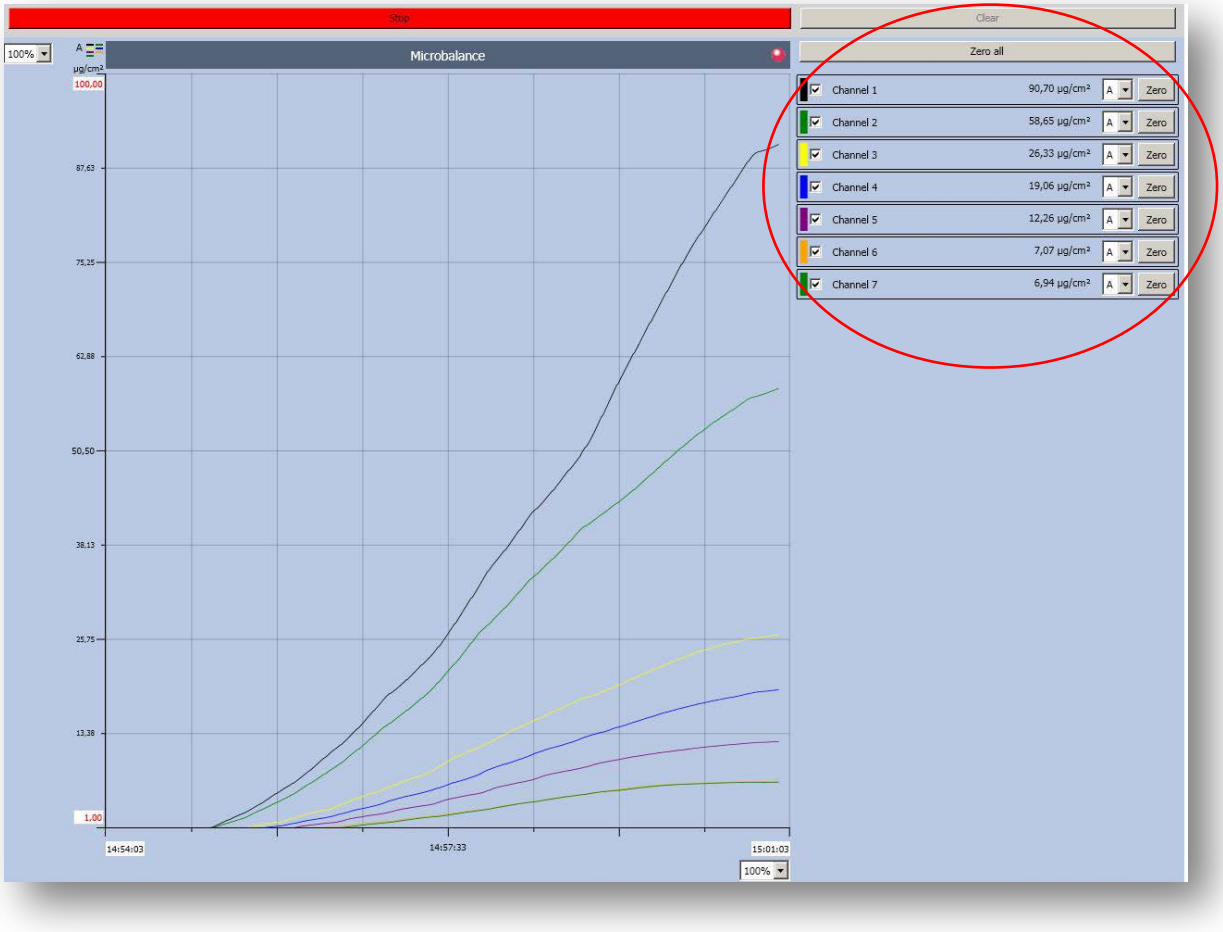


VITROCELL® 12 and 6
Microbalance Technology





VITROCELL® VC Monitor Software
Microbalance Application



VC Monitor Software Features:

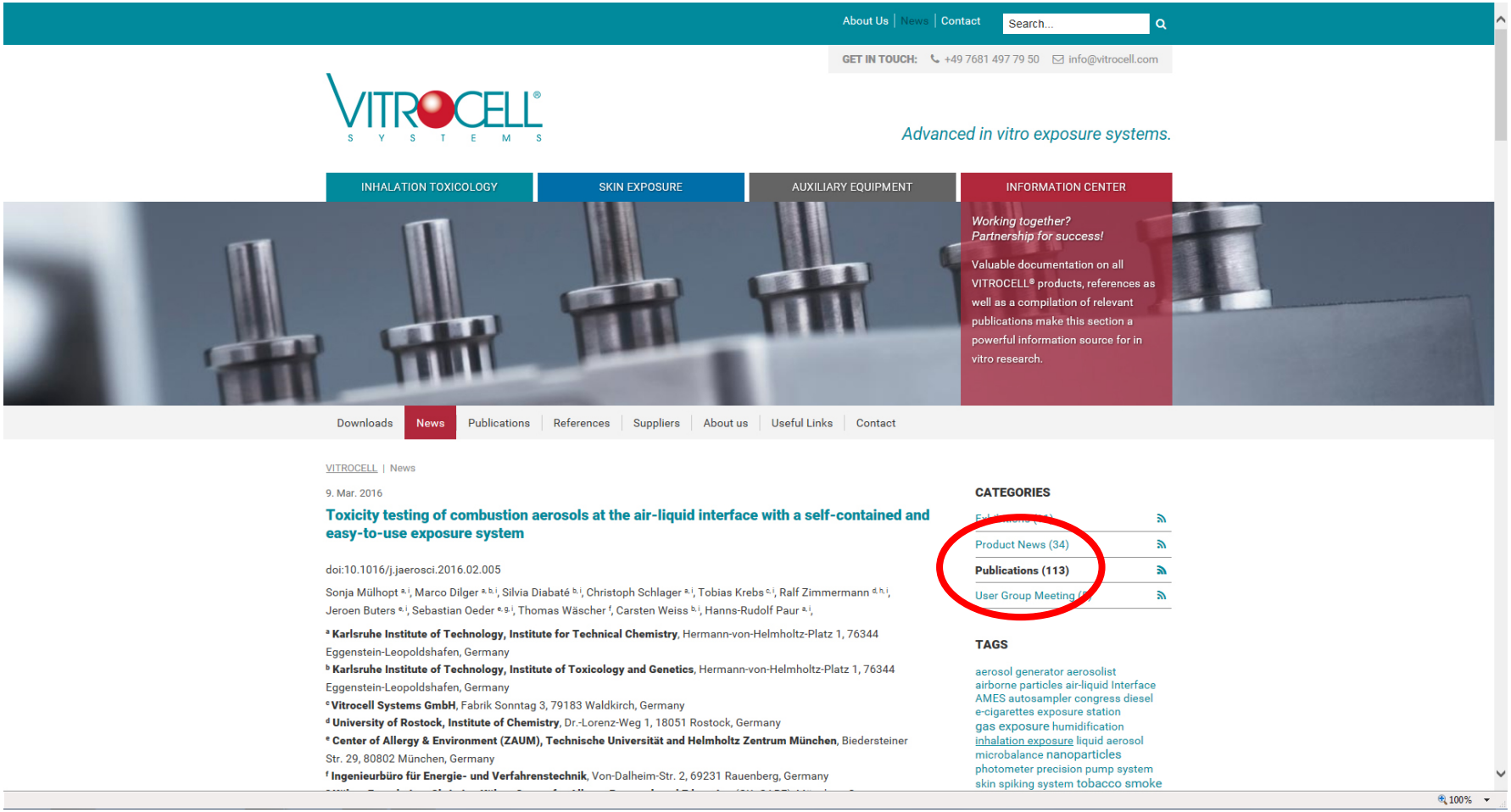
- *Up to eight Balances can be* displayed
- Online reading in ng/cm2
- Data Reporting in a MS excel executable format (*.csv)
- Checksum protected evaluation file
- GLP compliance

VITROCELL® VC Monitor Software
Photometer and Microbalance Combined

Combined view

VITROCELL® Publications

Please visit our website vitrocell.com and the „Publications“ chapter



Critical System Elements for *in vitro* Exposure to Conventional and E-cigarettes

- Smoke / Vapor generation
- Dilution for dose / response
- Exposure system
- Auxiliary equipment
- Dosimetry tools

Thank you for your attention !