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SOT MEETING 2019

A Six-Month Inhalation Study in ApoE-/- Mice to Investigate Cardiovascular and Respiratory Exposure Effects of E-Vapor Aerosols Compared with Cigarette Smoke

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Conflict of Interest Statement

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Aim

Assessment of Cardiovascular Effects following E-vapor and Conventional Cigarette Smoke Exposure in the ApoE$^{-/-}$ Mouse Model

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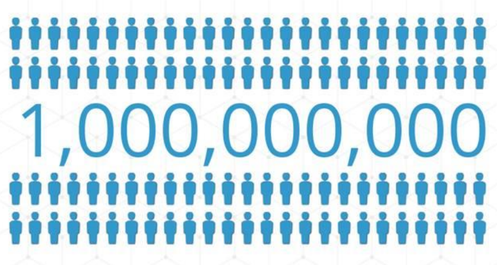
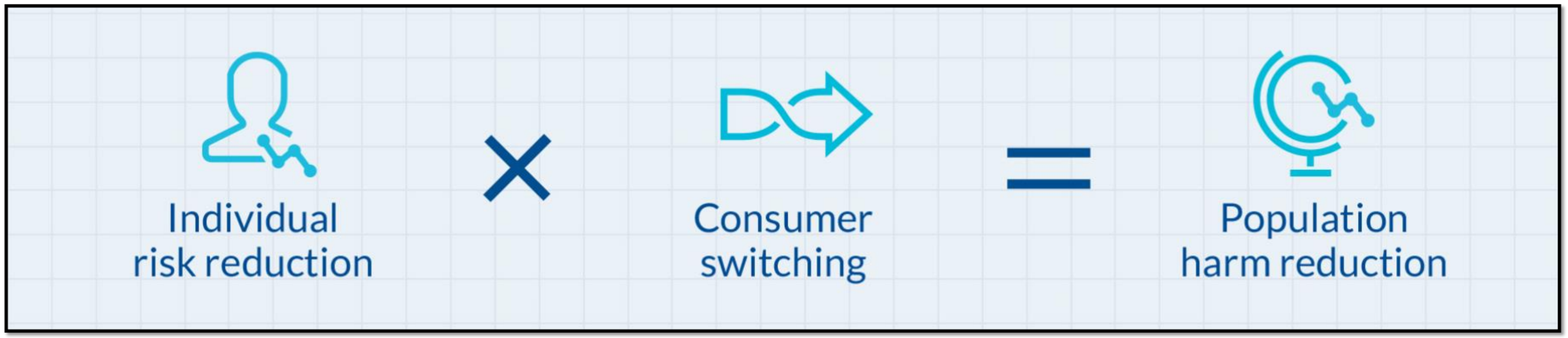
What Is the Objective of Harm Reduction?

- Smoking is addictive and causes a number of serious diseases
- Worldwide, it is estimated that more than **1 billion people** will continue to smoke in the foreseeable future*
- Offering smoke-free alternatives to adult smokers is a sensible, complementary addition to existing tobacco control strategies





Successful harm reduction requires that current adult smokers be offered a range of Reduced-Risk Products they can fully switched to, should they decide not to quit.

* http://www.who.int/tobacco/publications/surveillance/reportontrendstobaccosmoking/en/index4.html
Figure adapted from Clive Bates presentation to E-Cigarette Summit (19 Nov 2013)
Note: Reduced Risk Products ("RRPs") is the term PMI uses to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switched to these products versus continued smoking.

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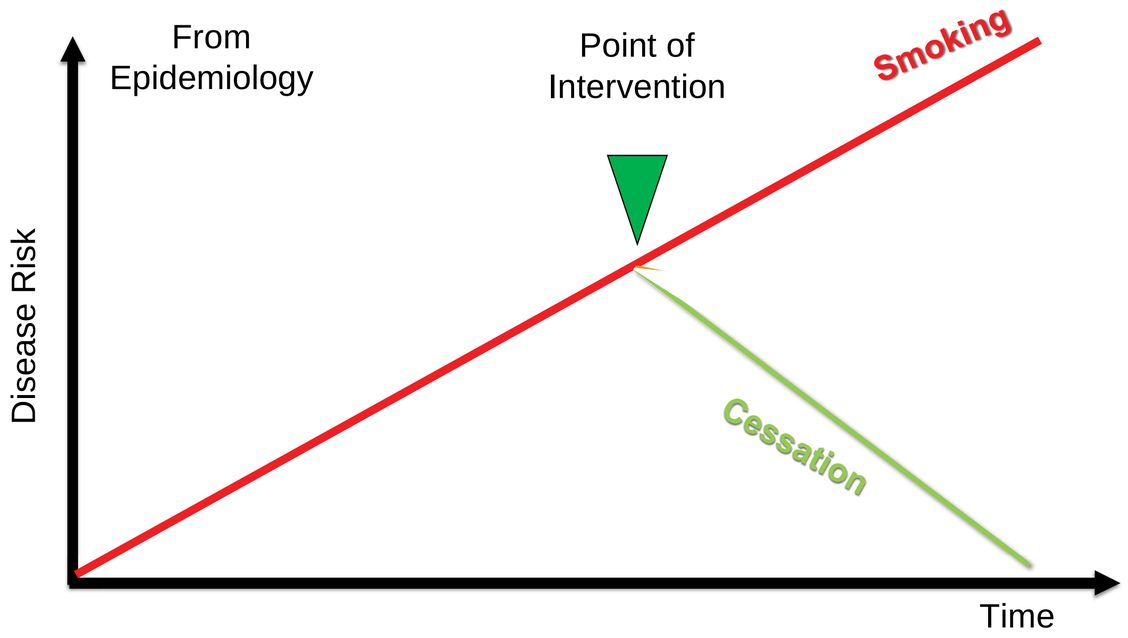
PMI's Scientific Assessment Approach

Assessment Framework



The assessement framework integrates what is known about combustible cigarette (CC) smoking and incorporates both epidemiological and mechanistic evidence to define the assessment approach.

These assessment steps are designed to provide five levels of evidence as the assessment program is completed.

Source: Smith, M.R., et al., Evaluation of the Tobacco Heating System 2.2. Part 1: Description of the system and the scientific assessment program. *Regulatory Toxicology and Pharmacology* (2016). http://dx.doi.org/10.1016/j.yrtph.2016.07.006

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Background

Electronic cigarettes are gaining popularity as a potential alternative to conventional cigarettes.

Most e-cigarette formulations contain vehicle (**propylene glycol (PG) and/or vegetable glycerin (VG)), nicotine and flavor ingredients.**

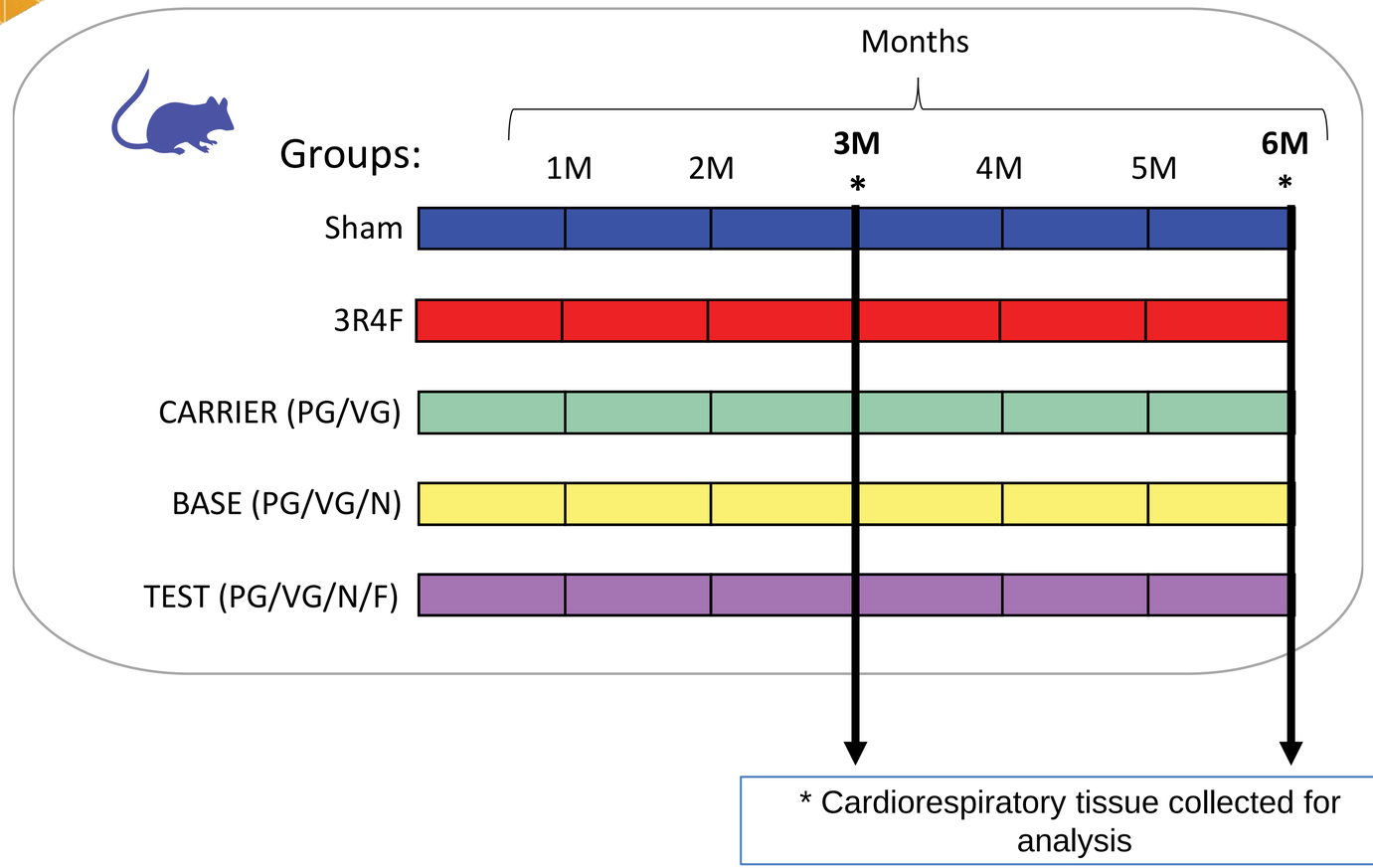
In contrast to 3R4F cigarette smoke (CS), e-cigarettes deliver nicotine without smoke constituents that arise from the combustion of tobacco.

Currently, there are limited data on the safety profile of e-cigarette usage in terms of **safety toxicology or disease risk assessment** as compared with that of conventional cigarette use.

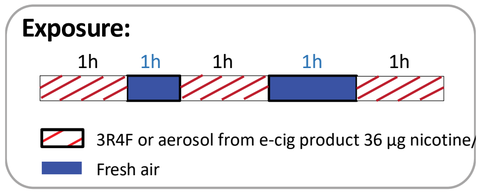
To support comprehensive assessment of exposure effects, the impact of PG/VG, nicotine as well as flavor constituents will be evaluated on the respiratory and cardiovascular systems of ApoE$^{-/-}$ mice.

A Six-Month Inhalation Study in ApoE$^{-/-}$ Mice to Investigate Cardiovascular and Respiratory Exposure Effects of E-Vapor Aerosols Compared with Cigarette Smoke

EXPERIMENTAL DESIGN



- Female ApoE$^{-/-}$ mice (12-14 weeks at initial dosing) were exposed to air (Sham), 3R4F cigarette smoke (CS), or E-vapor aerosols generated from CARRIER (PG/VG/water), BASE (CARRIER plus 4% nicotine), and TEST (BASE plus flavors) using CAG (capillary aerosol generator) system.
- ApoE$^{-/-}$ mice were exposed via whole body inhalation system for up to 3 hours/day, 5 days/week for 6 months.
- Fresh air breaks in-between 1h exposure



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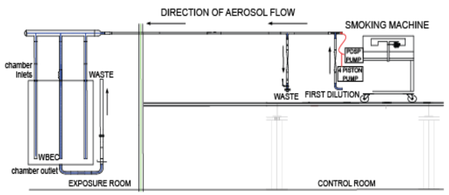
A Six-Month Inhalation Study in ApoE$^{-/-}$ Mice to Investigate Cardiovascular and Respiratory Exposure Effects of E-Vapor Aerosols Compared with Cigarette Smoke

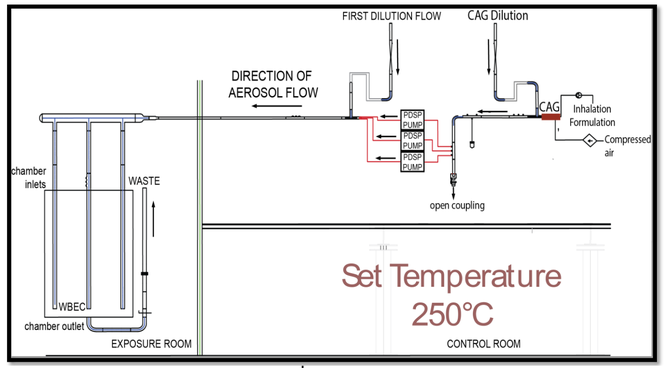
SMOKE MACHINE TO GENERATE CS FROM 3R4F



The 3R4F cigarettes were smoked according to the **Health Canada Intensive Smoking Protocol (Health_Canada, 1999)**.

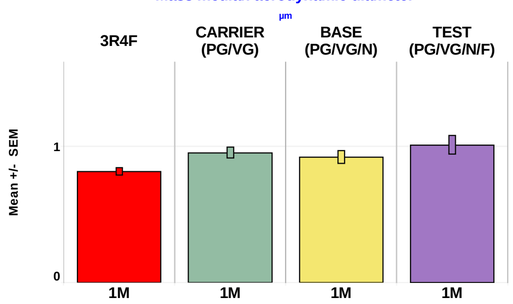
CAG (capillary aerosol generator) SYSTEM TO GENERATE E-VAPOR AEROSOLS

CAG system was successfully set up to generate and consistently deliver respirable E-Vapor aerosols to whole body mouse exposure system.



			CARRIER (PG/VG)	BASE (PG/VG/N)	TEST (PG/VG/N/F)
CAG temperature	6M	°C	250.03 (+/-) 1.7588	249.19 (+/-) 2.4670	249.74 (+/-) 1.6527

Mass median aerodynamic diameter



CAG was used to generate e-vapor from various e-liquids: "CARRIER" containing PG/VG alone, "BASE" containing PG/VG and 4% nicotine, and "TEST" containing PG/VG, 4% nicotine and flavors.

- -Target **TPM 600 µg/L**, for the 3R4F group.
- -PG/VG/N and PG/VG/N/F at matching nicotine concentration to 3R4F **35 µg/L.**

		Sham	3R4F	CARRIER (PG/VG)	BASE (PG/VG/N)	TEST (PG/VG/N/F)
Nicotine	µg/L	<LOD	35.15 (+/-) 4.8	<LOD	35.53 (+/-) 4.9	35.73 (+/-) 5.6
Total particulate matter	µg/L	-5.93 (+/-) 7.2	562.43 (+/-) 64.8	1 093.11 (+/-) 150.9	1 103.23 (+/-) 161.4	1 083.40 (+/-) 176.7

Gupta, R., et al., Investigation of a Novel Condensation Aerosol Generator: Solute and Solvent Effects. Aerosol Science and Technology, 2003. 37(8): p. 672-681.
Werley, M.S., et al., Non-clinical safety and pharmacokinetic evaluations of propylene glycol aerosol in Sprague-Dawley rats and Beagle dogs. Toxicology, 2011. 287(1-3): p. 76-9

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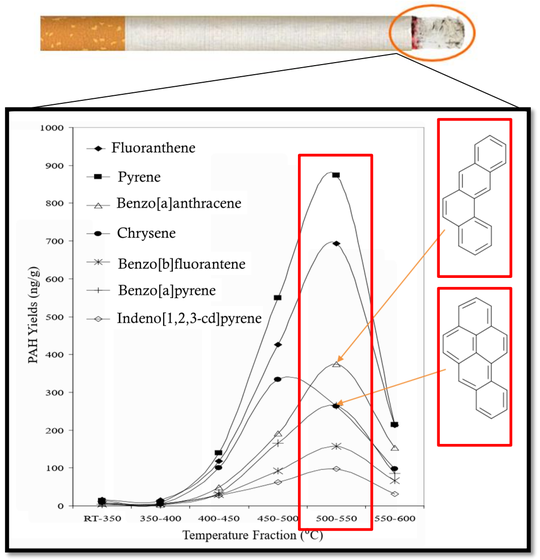
A Six-Month Inhalation Study in ApoE$^{-/-}$ Mice to Investigate Cardiovascular and Respiratory Exposure Effects of E-Vapor Aerosols Compared with Cigarette Smoke

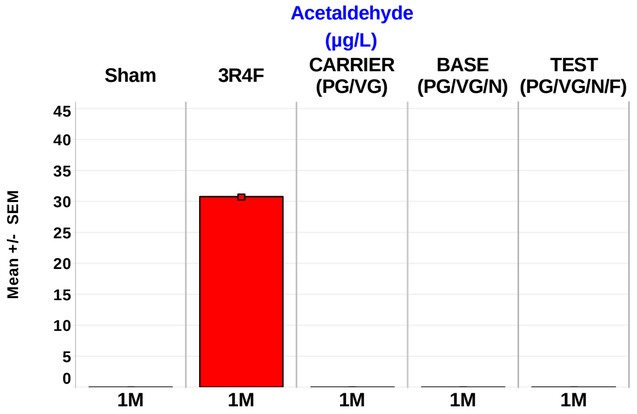
COMBUSTION IS A KEY

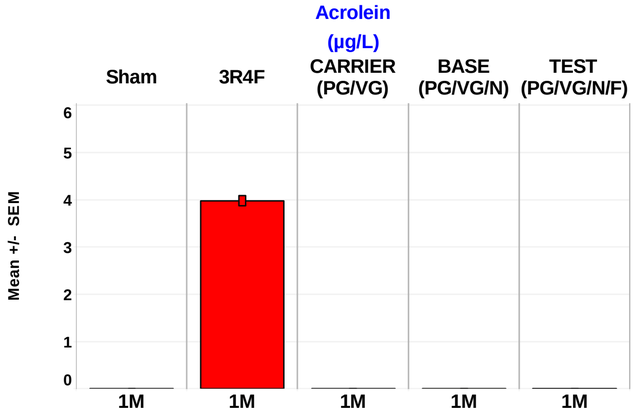
Scientific studies have shown that as the temperature of tobacco increases, the levels of harmful potentially harmful chemicals formed increases

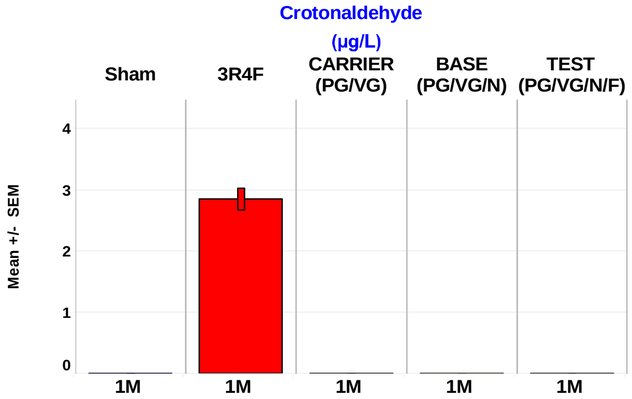


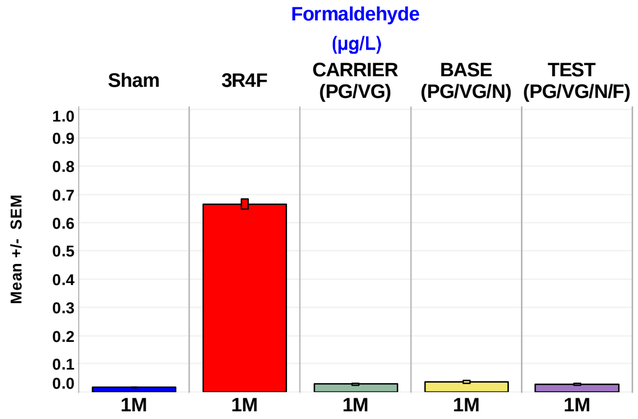
Source: McGrath, T.E., Wooten, J.B., Chan W.G. and Hajaligol, M.R., 2007, Formation of polycyclic Aromatic Hydrocarbons from Tobacco: the "Link" between Low Temperature Residual Solid and PAH Formation, Food and Chemical Toxicology, 45,6,1039-1050

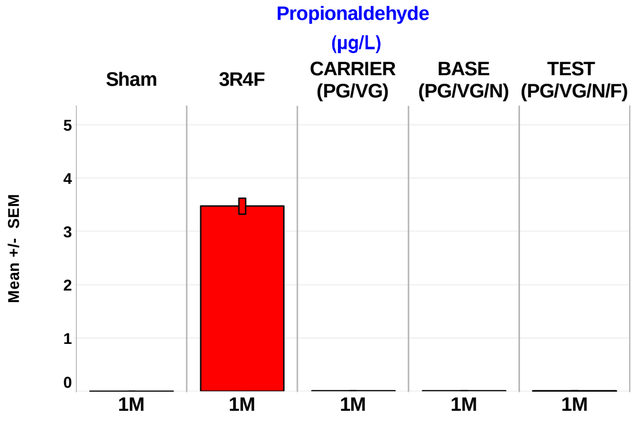
AEROSOL CONSTITUENTS IN TEST ATHMOSTHERE











Compared with cigarette smoke, the E-Vapor aerosol (CARRIER, BASE and TEST) present a lower level of harmful smoke constituents in the atmosphere.

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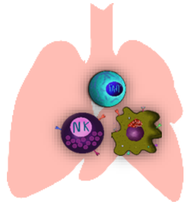
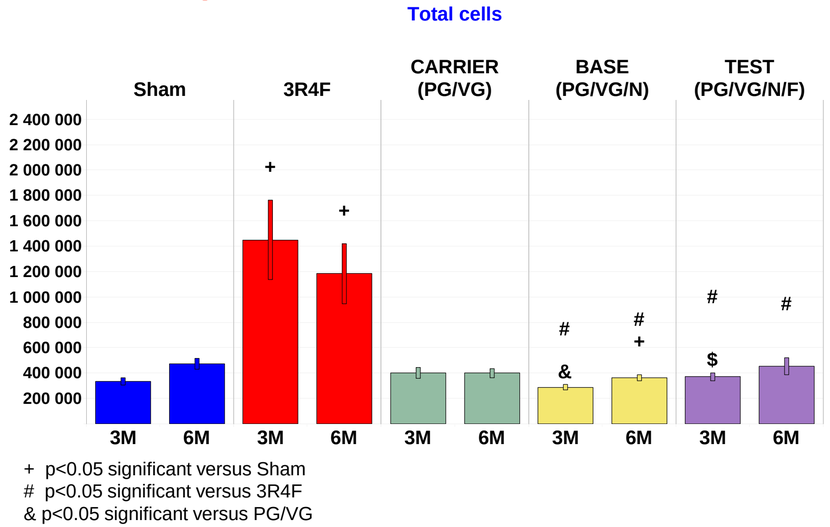
A Six-Month Inhalation Study in ApoE$^{-/-}$ Mice to Investigate Cardiovascular and Respiratory Exposure Effects of E-Vapor Aerosols Compared with Cigarette Smoke

Assessment of E-Vapor Aerosols in 6-Month ApoE$^{-/-}$ Mouse Study -- Lung Effects

LUNG INFLAMMATION



Cell-free BALF supernatants were analyzed using a multiplexed bead array



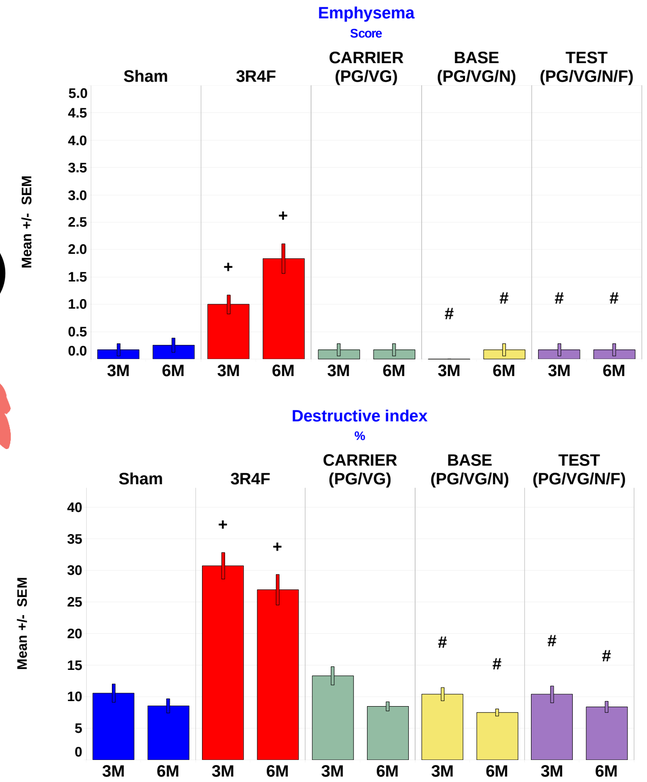
\+ p<0.05 significant versus Sham
\# p<0.05 significant versus 3R4F
& p<0.05 significant versus PG/VG

Endpoint_Name	3R4F 3M	3R4F 6M	CARRIER (PG/VG) 3M	CARRIER (PG/VG) 6M	BASE (PG/VG/N) 3M	BASE (PG/VG/N) 6M	TESTMIX (PG/VG/N/F) 3M	TESTMIX (PG/VG/N/F) 6M
G-CSF	3.59	2.72	0.74	0.50	0.82	0.52	0.78	1.09
GM-CSF	2.14	1.57	0.98	0.78	1.99	0.83	2.18	1.06
IFN-g	0.84	1.26	0.79	2.89	0.95	1.67	0.54	1.91
IL-1a	0.54	0.53	1.22	1.47	0.93	1.32	0.89	1.24
IL-1b	1.03	0.94	0.75	0.77	0.84	0.88	1.11	0.95
IL-2	0.49	0.68	1.05	1.29	0.92	1.11	0.79	0.98
IL-4	1.22	0.96	0.60	1.52	1.07	1.54	0.89	1.30
IL-5	1.68	0.87	1.30	2.01	0.93	0.98	1.24	0.83
IL-6	3.88	4.84	2.32	2.77	0.50	1.72	0.82	1.46
IL-7	0.52	0.74	0.97	0.69	0.92	1.07	1.05	0.56
IL-9	0.93	0.84	0.98	1.87	1.09	1.14	0.82	1.14
IL-10	0.32	0.29	1.05	1.04	0.70	0.94	0.63	0.72
IL-12	1.24	3.36	0.62	1.93	0.57	1.33	0.90	0.95
IL-12b	0.60	0.58	0.90	1.29	0.96	1.16	0.69	0.93
IL-13	0.63	0.85	0.70	2.06	0.96	1.25	0.77	1.28
IL-15	0.93	1.03	0.87	1.20	1.55	0.88	0.72	0.68
IL-17	1.79	2.70	0.58	1.55	0.49	0.65	0.56	2.11
IP-10	3.48	3.66	0.82	1.47	0.88	1.12	0.81	1.23
KC	4.99	8.20	0.66	1.09	0.63	1.02	0.61	1.73
MCP-1	6.15	4.77	1.05	0.62	1.04	0.88	1.30	0.60
MIP-1a	2.28	2.70	0.86	0.94	1.02	1.04	0.98	0.71
MIP-1b	10.52	12.82	1.02	0.90	1.39	1.57	0.80	1.48
MIP-2	1.06	0.85	0.91	1.25	0.95	0.88	1.04	1.09
MMP total	1.70	2.19	1.10	0.96	0.98	1.04	0.98	1.00
PECAM-1	1.24	1.07	1.09	0.88	0.83	1.01	0.74	1.04
pro-MMP-9	61.87	17.54	1.93	0.50	0.98	0.29	1.07	0.51
RANTES	0.55	0.79	0.65	1.69	0.77	0.91	0.83	0.96
sE-Selectin	1.04	0.88	0.84	2.66	0.92	0.91	0.89	1.01
sICAM1	2.23	2.13	1.08	0.98	0.97	0.93	1.05	0.89
sP-Selectin	0.94	1.04	0.89	1.26	0.92	0.98	1.18	0.86
Thrombomodulin	1.90	2.34	0.91	1.09	0.86	0.95	0.95	1.06
TNF-a	2.10	2.77	0.71	1.45	0.82	1.17	1.12	0.97
Total PAI-1	2.54	2.60	0.97	0.95	0.92	1.00	1.15	1.14

Compared with cigarette smoke, exposure to E-Vapor aerosols resulted in lower number of inflammatory cells in lung BALF.

Compared with cigarette smoke, exposure to E-Vapor aerosols resulted in lower level of inflammatory mediators.

LUNG STRUCTURAL DAMAGE



Compared with cigarette smoke, histopathological semi-quantitative scoring shows that exposure to E-Vapor aerosols resulted in lower emphysematous changes in lung.

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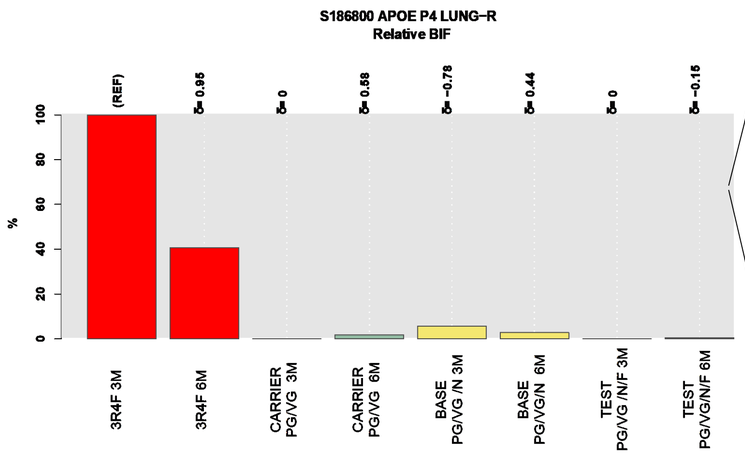
A Six-Month Inhalation Study in ApoE$^{-/-}$ Mice to Investigate Cardiovascular and Respiratory Exposure Effects of E-Vapor Aerosols Compared with Cigarette Smoke

Assessment of E-Vapor Aerosols in 6-Month ApoE$^{-/-}$ Mouse Study -- Lung Effects

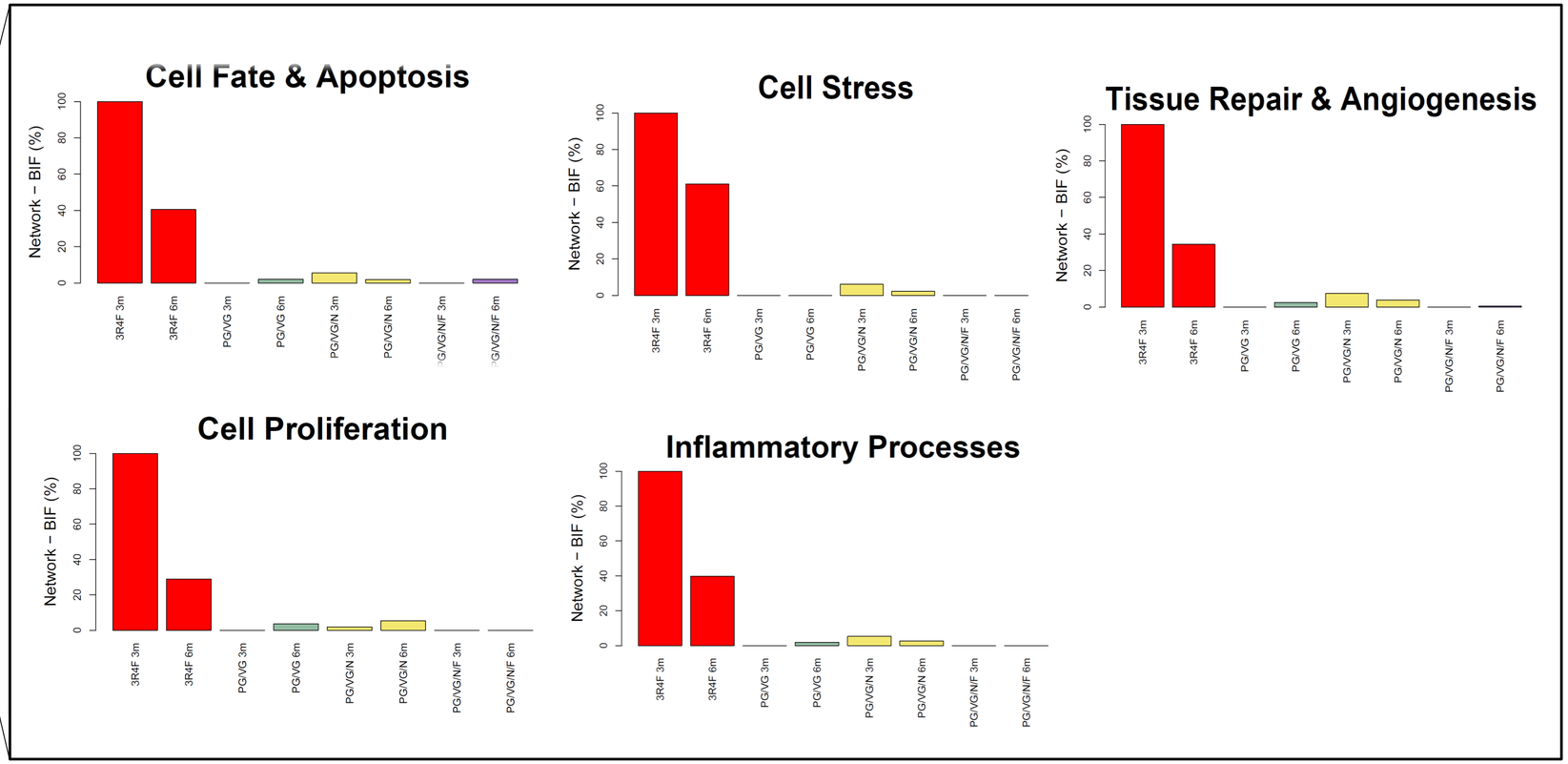
LUNG MOLECULAR CHANGES

Differentially expressed genes in lung

	Group of Mice		3R4F		PG/VG		PG/VG/N		PG/VG/N/F	
Target	Tissue	TimePoint	3	6	3	6	3	6	4	6
	LUNG-R	Up	848	351	0	0	0	0	0	0
		Down	477	93	0	0	0	0	0	0



Compared with cigarette smoke, exposure to E-Vapor aerosols resulted in lower molecular changes in lung tissue.

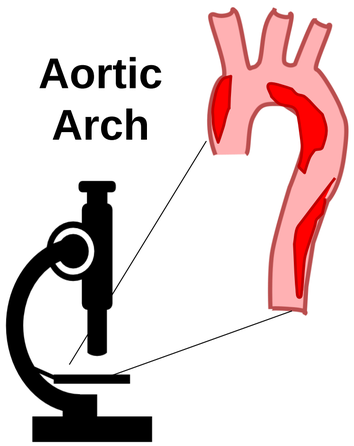


Compared with cigarette smoke, exposure to E-Vapor aerosols induced significantly less molecular changes related to stress responses, cell proliferation and inflammation in lung tissue.

A Six-Month Inhalation Study in ApoE$^{-/-}$ Mice to Investigate Cardiovascular and Respiratory Exposure Effects of E-Vapor Aerosols Compared with Cigarette Smoke

Cardiovascular Disease

- Atherosclerosis is an inflammatory disease characterized by the accumulation of lipoprotein and leucocytes as plaque in the arterial layer. Uncontrolled, it can lead to coronary heart disease (CHD) and underlying clinical events such as heart attack or angina.
- Development of CHD is accelerated by a variety of risk factors, including male gender, smoking, dyslipidemia, elevated blood pressure, physical inactivity, obesity and diabetes.
- Patients witch COPD have increased cardiovascular morbidity and mortality.



The ApoE$^{-/-}$ mouse model permits the concomitant evaluation of:

Emphysema (COPD)
- Lung function
- Pulmonary inflammation
- Pathology

Cardiovascular disease
- Clinical chemistry
- Plaque development


TOXICOLOGICAL SCIENCES, 149(2), 2016, 411–4.
doi: 10.1093/toxsci/kfv243
Advance Access Publication Date: November 25, 2015
Research Article

An 8-Month Systems Toxicology Inhalation/Cessation Study in Apoe$^{-/-}$ Mice to Investigate Cardiovascular and Respiratory Exposure Effects of a Candidate Modified Risk Tobacco Product, THS 2.2, Compared With Conventional Cigarettes


TOXICOLOGICAL SCIENCES, 149(2), 2016, 441–457
doi: 10.1093/toxsci/kfv244
Advance Access Publication Date: November 17, 2015
Research Article

Effects of Cigarette Smoke, Cessation, and Switching to Two Heat-Not-Burn Tobacco Products on Lung Lipid Metabolism in C57BL/6 and Apoe$^{-/-}$ Mice—An Integrative Systems Toxicology Analysis


Contents lists available at ScienceDirect
Food and Chemical Toxicology
journal homepage: www.elsevier.com/locate/foodchemtox

Aerosol from Tobacco Heating System 2.2 has reduced impact on mouse heart gene expression compared with cigarette smoke

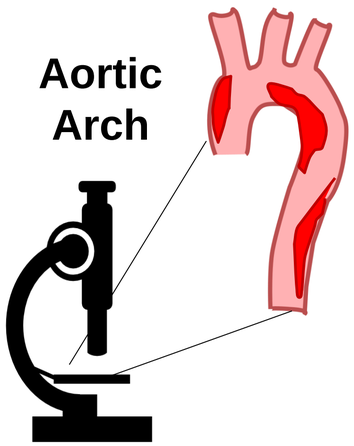
https://intervals.science"

Lo Sasso, G., Schlage, W.K., Boue, S., Veljkovic, E., Peitsch, M.C. and Hoeng, J. (2016): The Apoe(-/-) mouse model: a suitable model to study cardiovascular and respiratory diseases in the context of cigarette smoke exposure and harm reduction. Journal of translational medicine, 14, 146.

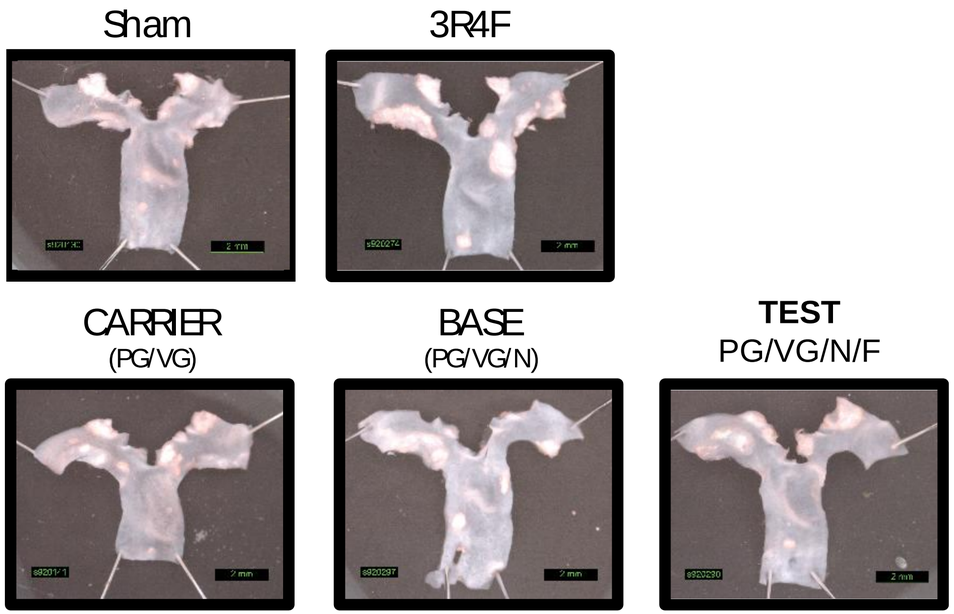
A Six-Month Inhalation Study in ApoE$^{-/-}$ Mice to Investigate Cardiovascular and Respiratory Exposure Effects of E-Vapor Aerosols Compared with Cigarette Smoke

The effect of 3R4F CS and E-Vapor aerosols on atherosclerotic plaque formation

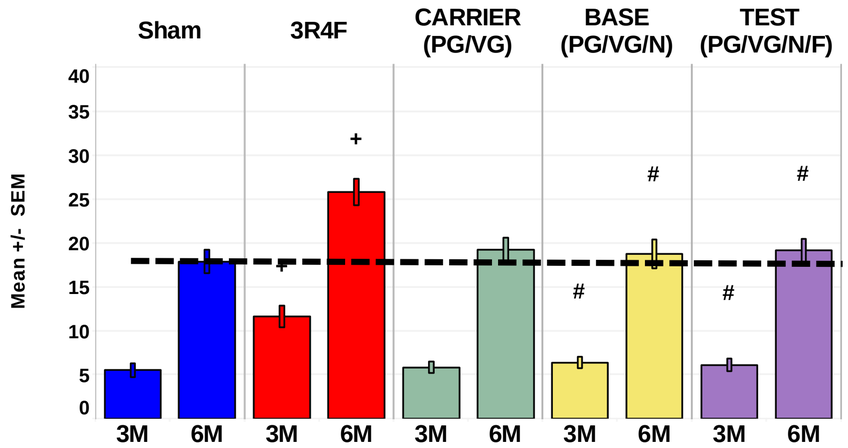
STRUCTURAL DAMAGE



6 Months



Percentage of plaque (%)



\+ p<0.05 significant versus Sham
\# p<0.05 significant versus 3R4F

Compared with cigarette smoke, exposure to E-Vapor aerosols (CARRIER, BASE and TEST) induced lower atherosclerotic plaque formation.

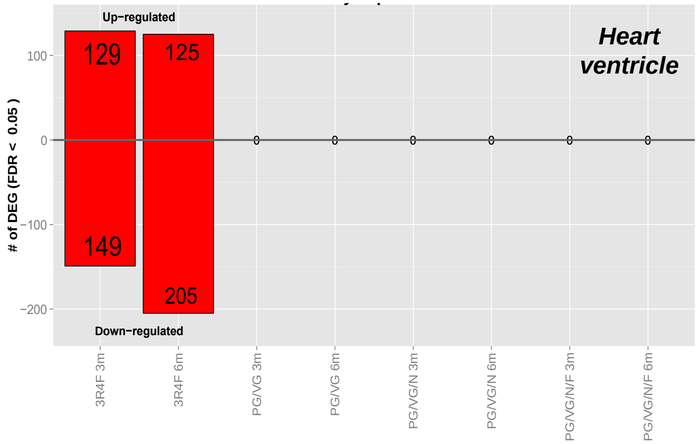
There was no difference in plaque area in animals exposed to CARRIER, BASE and TEST aerosol for six months compared to the fresh air-treated animals.

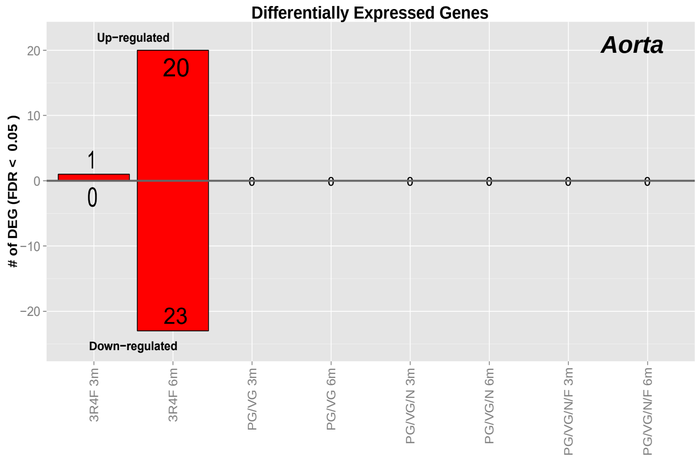
A Six-Month Inhalation Study in ApoE$^{-/-}$ Mice to Investigate Cardiovascular and Respiratory Exposure Effects of E-Vapor Aerosols Compared with Cigarette Smoke

The effect of 3R4F CS and E-Vapor aerosols on heart ventricle

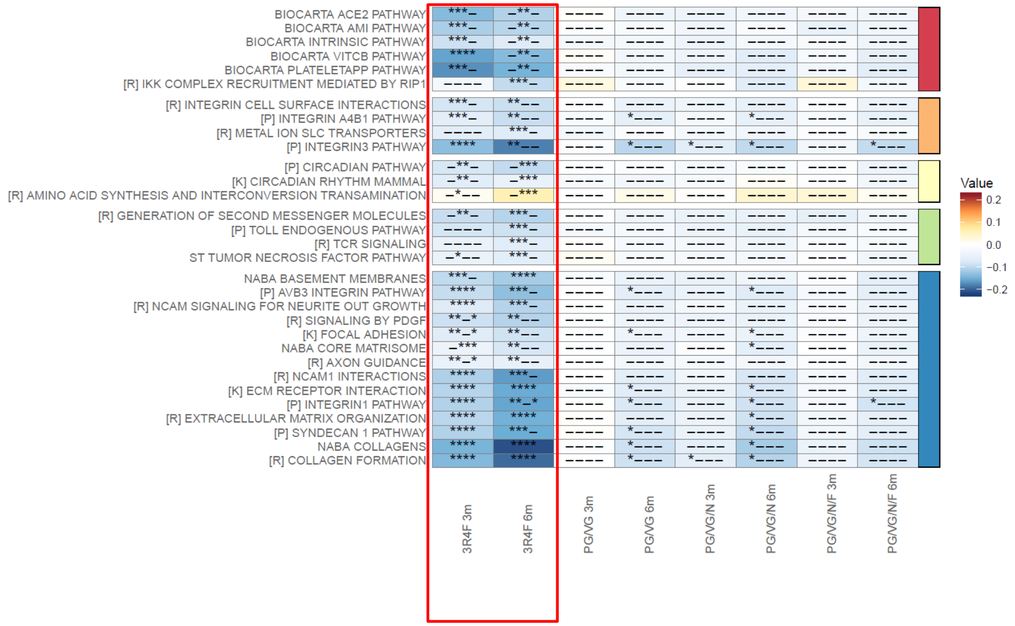
MOLECULAR ANALYSIS

Differentially expressed genes

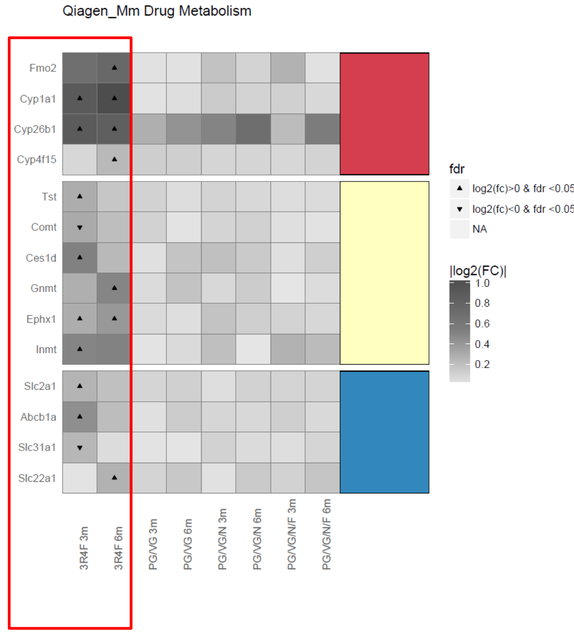




ECM RECEPTOR INTERACTION



DRUG METABOLISM



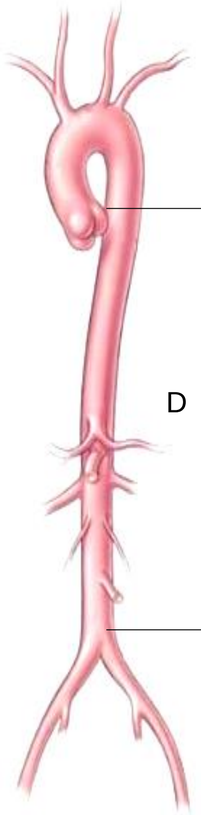
Compared with cigarette smoke, exposure to E-Vapor aerosols (CARRIER, BASE and TEST) lower molecular changes in aorta and heart tissue (e.g., including mechanisms reflecting stress responses and those linked to the extracellular matrix).

A Six-Month Inhalation Study in ApoE$^{-/-}$ Mice to Investigate Cardiovascular and Respiratory Exposure Effects of E-Vapor Aerosols Compared with Cigarette Smoke

The effect of 3R4F CS and E-Vapor aerosols on carotid and abdominal artery

ASSESSEMENT OF ARTERIES FUNCTION

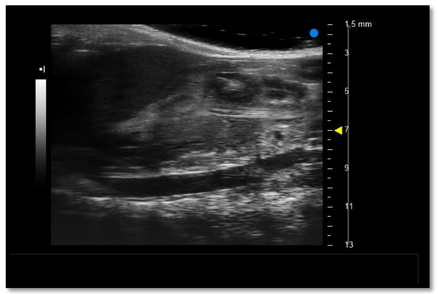
PWV= Distance/Time



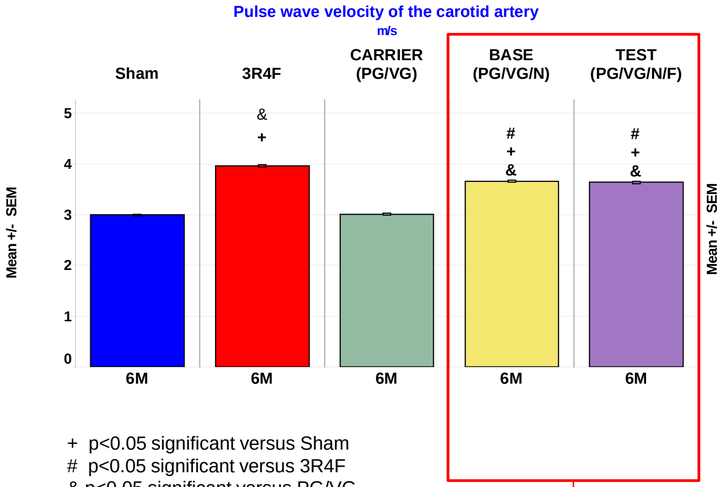
High speed:
Indicates high blood pressure and stiff arteries.

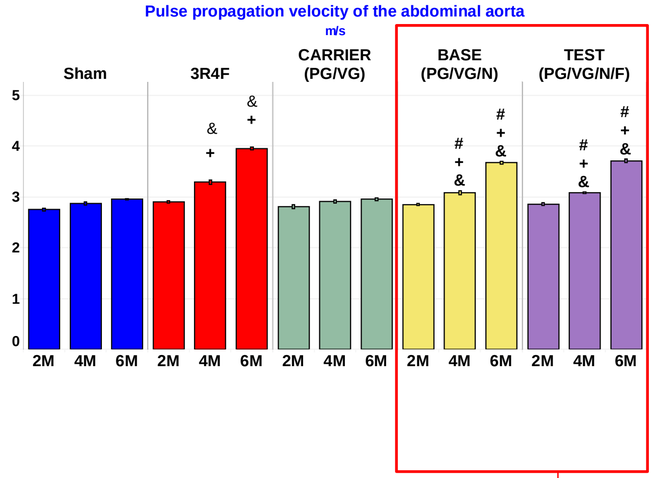
Low speed:
Indicates low blood pressure and elastic arteries.

ULTRASOUND VEVO 3100 system



Pulse Wave Velocity (PWV) is depending on physical properties of the vessels, and especially on their STIFFNESS.





Nicotine

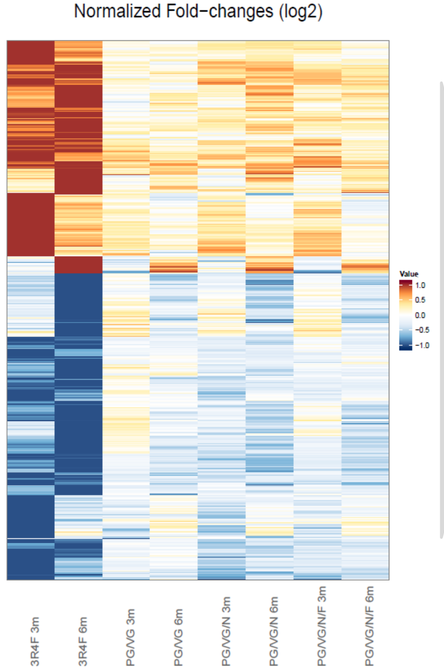
The nicotine-containing liquid aerosols induce significantly less arterial stiffness than cigarette smoke.

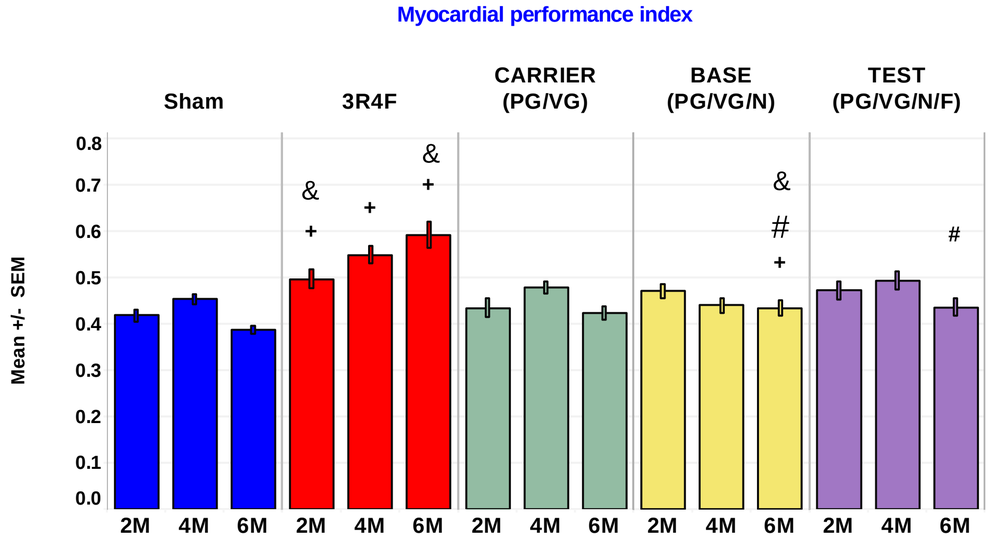
A Six-Month Inhalation Study in ApoE$^{-/-}$ Mice to Investigate Cardiovascular and Respiratory Exposure Effects of E-Vapor Aerosols Compared with Cigarette Smoke

The effect of 3R4F CS and E-Vapor aerosols on heart

ASSESSEMENT OF HEART FUNCTION

Molecular changes in the heart





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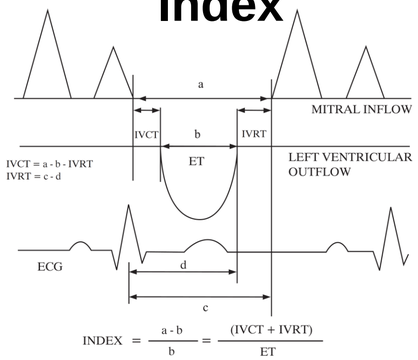
\# p<0.05 significant versus 3R4F
& p<0.05 significant versus PG/VG

MPI
Myocardial Performance Index



Detects early alterations of LV systo-diastolic performance

Compared with cigarette smoke, exposure to E-Vapor aerosols resulted in less effects on Myocardial Performance Index, which detects early alterations of systo-diastolic performance of left ventricle

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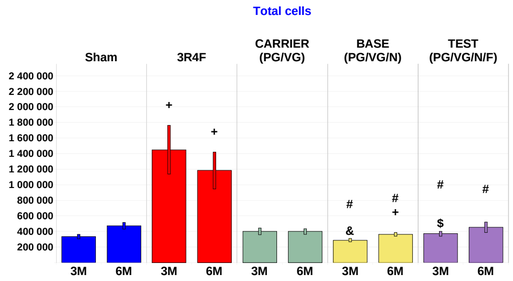
Summary

Compared with cigarette smoke, exposure to E-Vapor aerosols resulted in:

LUNG INFLAMMATION

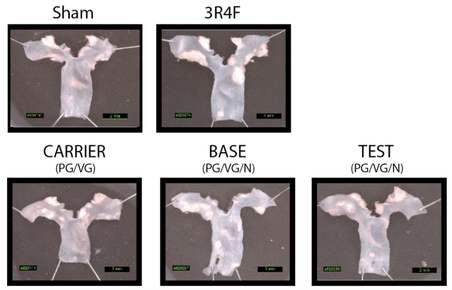
Total Lung



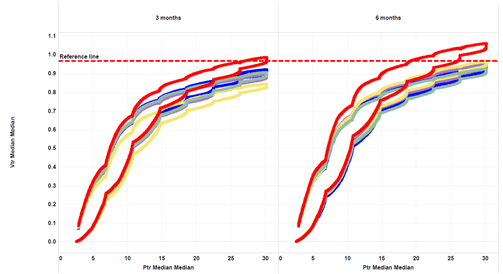
Mediators in BALF

	3R4F		BASE (PG/VG/N)		CARRIER (PG/VG)		TESTMIX (PG/VG/N/F)	
Endpoint_Name	3M	6M	3M	6M	3M	6M	3M	6M
G-CSF	3.59	2.72	0.82	0.52	0.74	0.50	0.78	1.09
GM-CSF	2.14	1.57	1.99	0.83	0.98	0.78	2.18	1.06
IFN-g	0.84	1.26	0.95	1.67	0.79	2.89	0.54	1.91
IL-1a	0.54	0.53	0.93	1.32	1.22	1.47	0.89	1.24
IL-1b	1.03	0.94	0.84	0.88	0.75	0.77	1.11	0.95
IL-2	0.49	0.68	0.92	1.11	1.05	1.29	0.79	0.98
IL-4	1.22	0.96	1.07	1.54	0.60	1.52	0.89	1.30
IL-5	1.68	0.87	0.93	0.98	1.30	2.01	1.24	0.83
IL-6	3.88	4.84	0.50	1.72	2.32	2.77	0.82	1.46
IL-7	0.52	0.74	0.92	1.07	0.97	0.69	1.05	0.56
IL-9	0.93	0.84	1.09	1.14	0.98	1.87	0.82	1.14
IL-10	0.32	0.29	0.70	0.94	1.05	1.04	0.63	0.72
IL-12	1.24	3.36	0.57	1.33	0.62	1.93	0.90	0.95
IL-12b	0.60	0.58	0.96	1.16	0.90	1.29	0.69	0.93
IL-13	0.63	0.85	0.96	1.25	0.70	2.06	0.77	1.28
IL-15	0.93	1.03	1.55	0.88	0.87	1.20	0.72	0.68
IL-17	1.79	2.70	0.49	0.65	0.58	1.55	0.56	2.11
IP-10	3.48	3.66	0.88	1.12	0.82	1.47	0.81	1.23
KC	4.99	8.20	0.63	1.02	0.66	1.09	0.61	1.73
MCP-1	6.15	4.77	1.04	0.88	1.05	0.62	1.30	0.60
MIP-1a	2.28	2.70	1.02	1.04	0.86	0.94	0.98	0.71
MIP-1b	10.52	12.88	1.39	1.57	1.02	0.90	0.80	1.48
MIP-2	1.06	0.85	0.95	0.88	0.91	1.25	1.04	1.09
MMP total	1.70	2.19	0.98	1.04	1.10	0.96	0.98	1.00
PECAM-1	1.24	1.07	0.83	1.01	1.09	0.88	0.74	1.04
pro-MMP-9	61.87	17.54	0.98	0.29	1.93	0.50	1.07	0.51
RANTES	0.55	0.79	0.77	0.91	0.65	1.69	0.83	0.96
sE-Selectin	1.04	0.88	0.92	0.91	0.84	2.66	0.89	1.01
sICAM1	2.23	2.13	0.97	0.93	1.08	0.98	1.05	0.89
sP-Selectin	0.94	1.04	0.92	0.98	0.89	1.26	1.18	0.86
Thrombomodulin	1.90	2.30	0.86	0.95	0.91	1.09	0.95	1.06
TNF-a	2.10	2.77	0.82	1.17	0.71	1.45	1.12	0.97
Total PAI-1	2.54	2.60	0.92	1.00	0.97	0.95	1.15	1.14

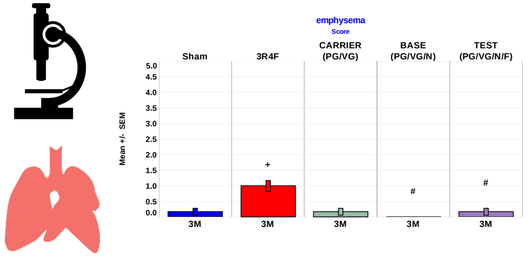
CARDIOVASCULAR



LUNG FUNCTION



LUNG HISTOPATHOLOGY



Biomarkers/Endpoints		CARRIER (PG/VG)	BASE (PG/VG/N)	TEST (PG/VG/N/F)
HPHC	*Acrolein*	⬇	⬇	⬇
	Acetaldehyde	⬇	⬇	⬇
	Formaldehyde	⬇	⬇	⬇
	Propionaldehyde	⬇	⬇	⬇
	Crotonaldehyde	⬇	⬇	⬇
	4-(methylnitrosamino)1-(3-pyridyl)-1-butanone	⬇	⬇	⬇
	N-Nitrosonornicotine	⬇	⬇	⬇
Cardio vascular disease	*The rate of atherosclerotic plaque growth*	⬇	⬇	⬇
	Transcriptomics analysis of the aorta - molecular dysregulation	⬇	⬇	⬇
	Red blood cells - Hematocrite level	⬇	⬇	⬇
	Platelets level	⬇	⬇	⬇
	Pulse wave velocity (carotid artery)	⬇	➡	➡
	Transcriptomics analysis of the heart ventricle - molecular dysregulation	⬇	⬇	⬇
	Systolic-Diastolic dysfunctiom -Myocardial performance index	⬇ ⬇	⬇ ⬇	⬇ ⬇
Respiratory disease	*Lung inflammation-inflammatory cells in BALF*	⬇	⬇	⬇
	Lung inflammation-inflammatory mediators	⬇	⬇	⬇
	Lung function measured using FlexiVent system	⬇	⬇	⬇
	Lung emphysematous changes	⬇	⬇	⬇
	Transcriptomics analysis of the lung -molecular dysregulation of xenobiotic metabolism, inflammation, hypoxia apoptosis, cell proliferation.	⬇	⬇	⬇
	Transcriptomics analysis of the RNE -molecular dysregulation of xenobiotic metabolism, inflammation, hypoxia apoptosis, cell proliferation.	⬇	⬇	⬇

In comparison to 3R4F cigarette smoke e-vapor aerosols:

- ✓ Lower the level of inflammatory cells and mediators
- ✓ Lower atherosclerotic plaque formation
- ✓ Lower emphysematous changes in lung

This study suggests that E-Vapor aerosols induce significantly lower biological responses associated with smoking-related cardiovascular and pulmonary diseases.

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IBL GROUP HOME
IBL Immuno-Biological Laboratories Co., Ltd.

ABF ANALYTISCH-BIOLOGISCHES FORSCHUNGSLABOR MÜNCHEN

LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG

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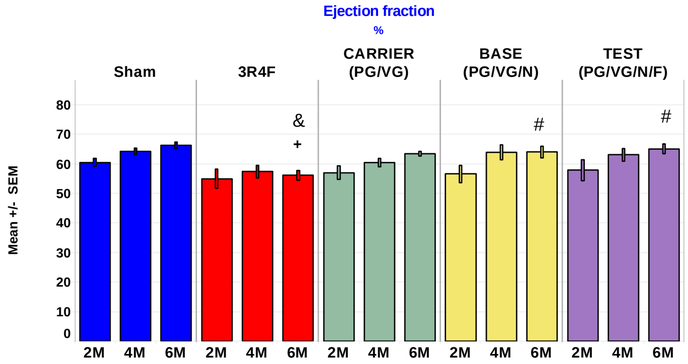
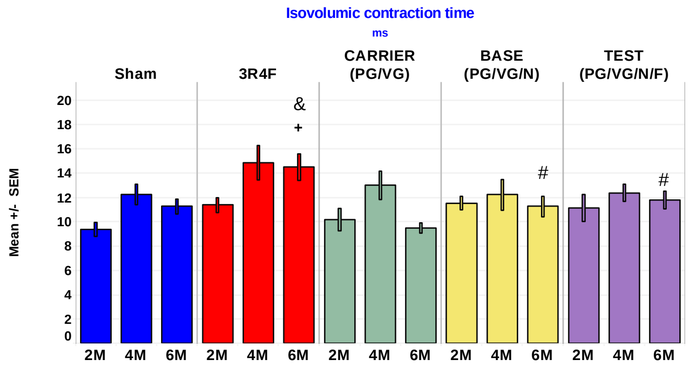
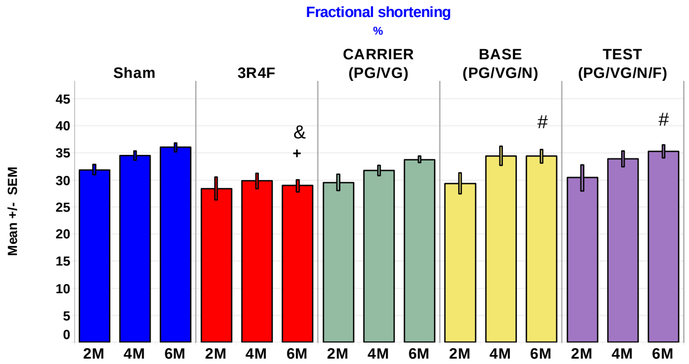
Thank you for your attention

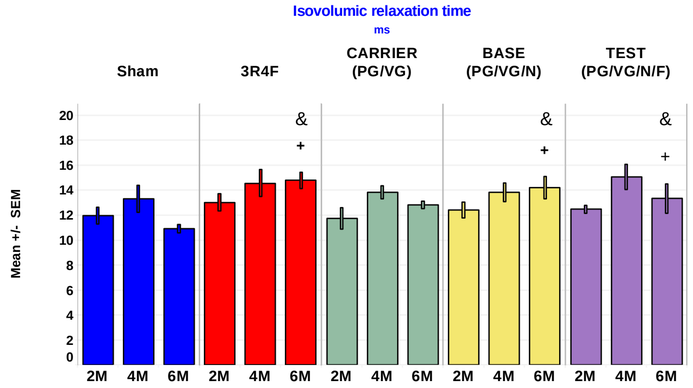
A Six-Month Inhalation Study in ApoE$^{-/-}$ Mice to Investigate Cardiovascular and Respiratory Exposure Effects of E-Vapor Aerosols Compared with Cigarette Smoke

Back up slide









\+ p<0.05 significant versus Sham
\# p<0.05 significant versus 3R4F
& p<0.05 significant versus PG/VG

Compared with cigarette smoke, exposure to E-Vapor aerosols resulted in lower effects on:
EF(Ejection fraction)
FS (Fractional shorteneing)
IVCT (Isovolumic contraction time)
IVRT (Isovolumic relaxation time)

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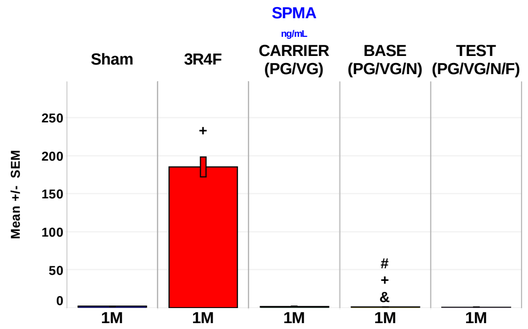
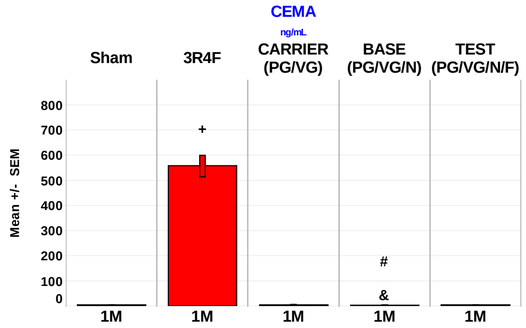
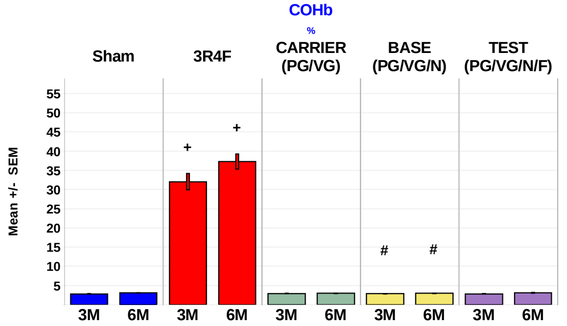
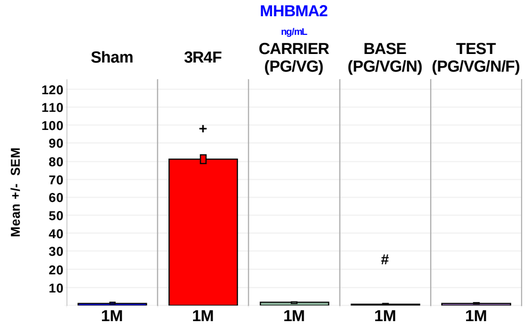
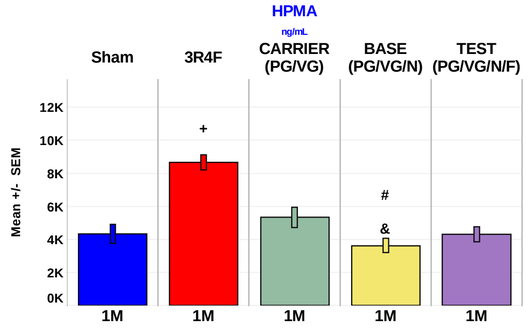
Back up slide

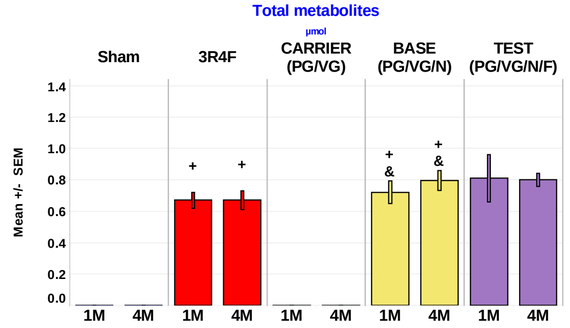












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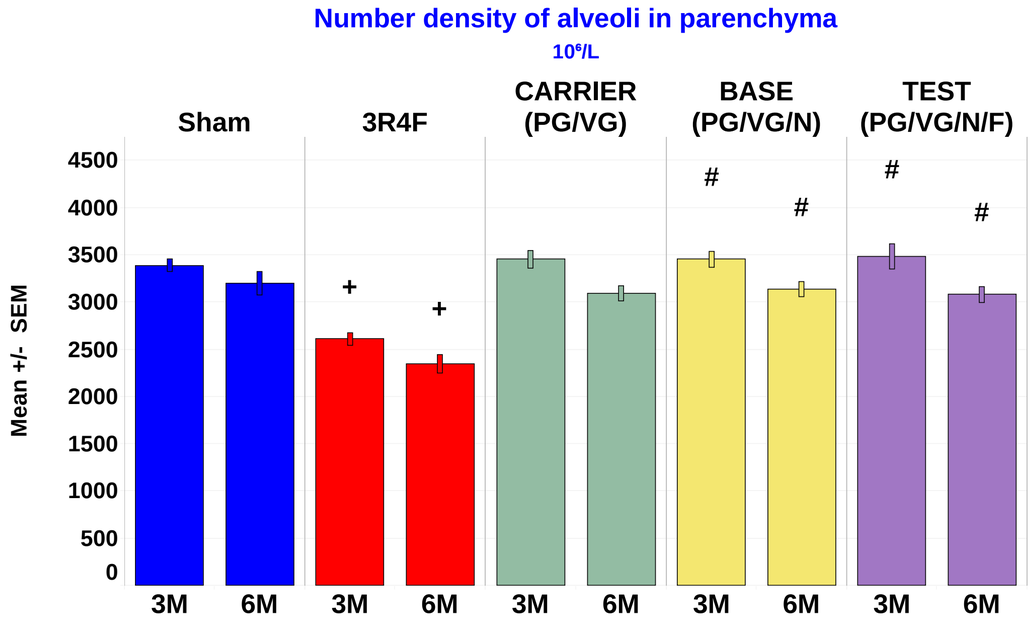
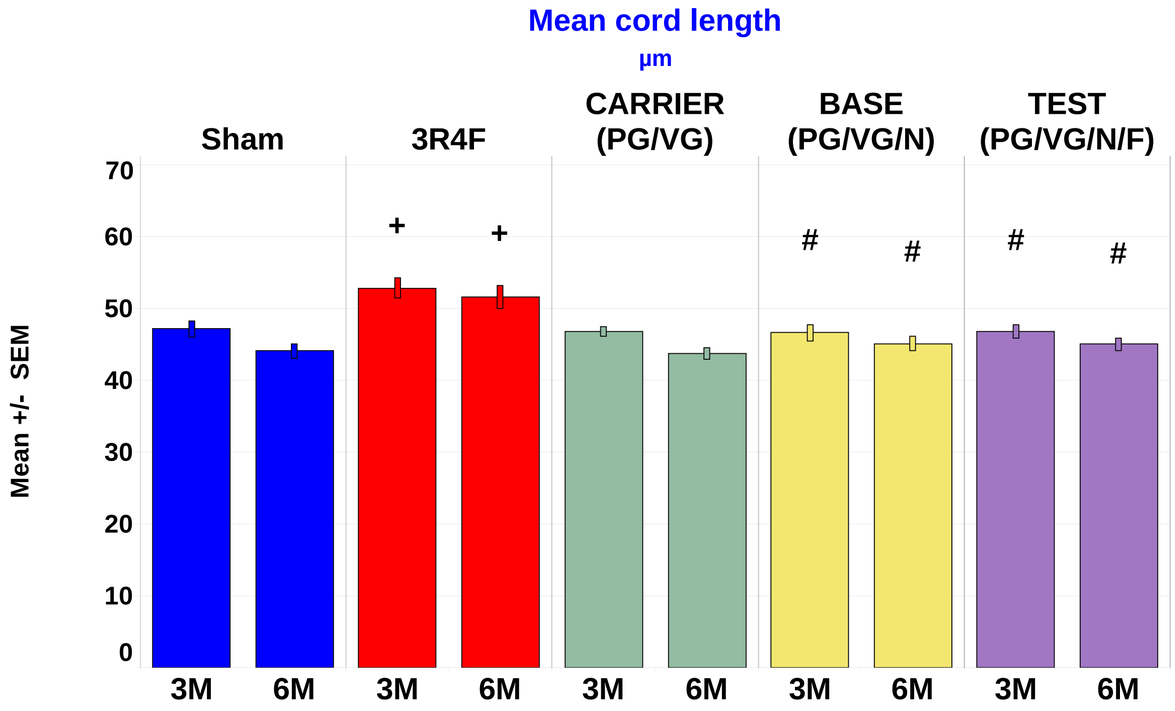
Back up slide





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