EVIDENCE RELATED TO THE HEALTH RISK OF *IQOS* USE

EVALUATION OF NONCLINICAL STUDIES

Presented by
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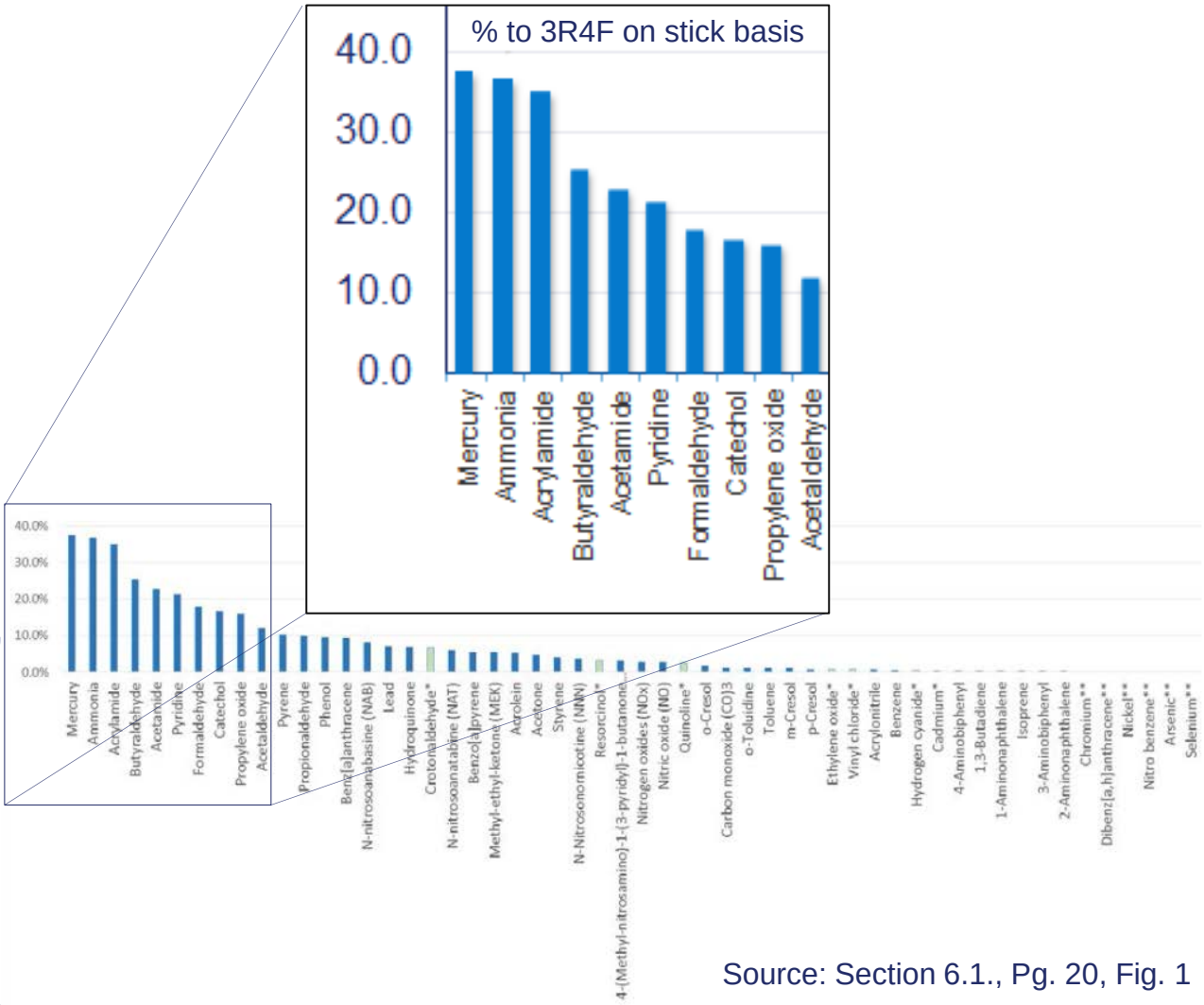
OUTLINE

- Chemicals found in *HeatStick* aerosols and reference cigarette smoke, including harmful and potentially harmful constituents
- In vitro studies
  - Cytotoxicity and mutagenicity studies
  - Organotypic studies
- In vivo studies
  - 90-day rat inhalation studies
  - 8-month cessation and switching study with ApoE -/- mice
  - Carcinogenicity study with A/J mice

TOXICOLOGICAL EVALUATION OF HPHCS IN REFERENCE CIGARETTE SMOKE AND *HEATSTICK* AEROSOLS

Many HPHC levels in *HeatStick* aerosols are reduced compared to reference cigarette smoke. However, consuming 10 *HeatSticks* exposes users to levels of mercury, ammonia, acrylamide, butyraldehyde, acetamide, pyridine, formaldehyde, catechol, propylene oxide, and acetaldehyde that are comparable to smoking 1-3 reference cigarettes.



Source: Section 6.1., Pg. 20, Fig. 1

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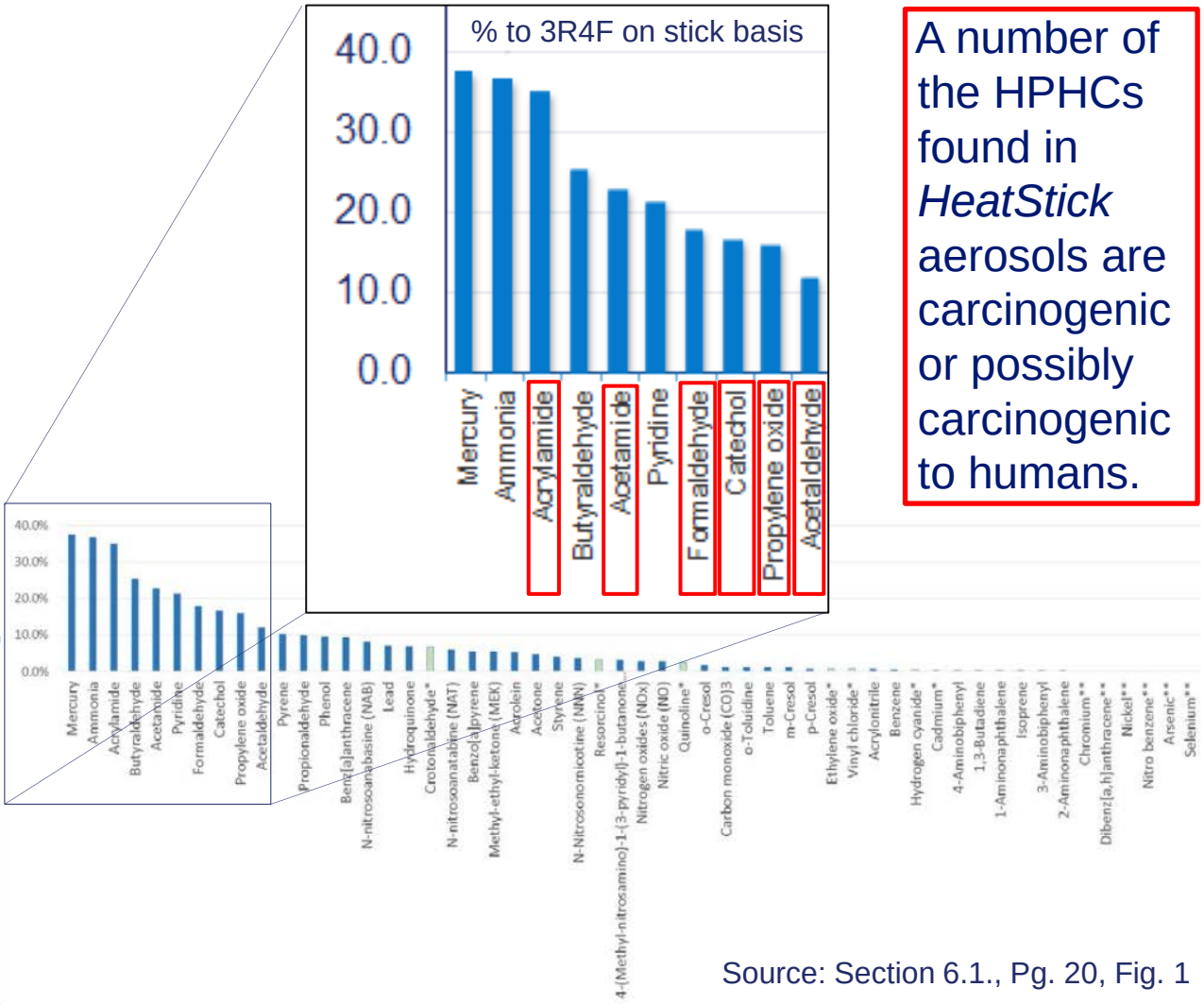


A number of the HPHCs found in *HeatStick* aerosols are carcinogenic or possibly carcinogenic to humans.

Source: Section 6.1., Pg. 20, Fig. 1

TOXICOLOGICAL EVALUATION OF REFERENCE CIGARETTE SMOKE AND *HEATSTICK* AEROSOLS

The applicant has recently submitted data identifying at least 12 possibly carcinogenic or genotoxic chemicals that are found at higher levels in *HeatStick* aerosols than in reference cigarette smoke.

- For carcinogens that are mutagenic, cancer potency is assessed using a linear extrapolation from the low-dose region of the dose-response curve. Using this model, any increased exposure increases cancer risk.

CAS#	Chemical	Fold Increase over 3R4F Cigarette	Designation
98-00-0	2-Furanmethanol	6.8	Possibly Carcinogenic
96-24-2	3-chloro-1,2-Dihydroxyropane	5.7	Possibly Carcinogenic
556-52-5	Glycidol	3.2	Probably Carcinogenic
98-01-1	Furfural	1.6	Possibly Carcinogenic
128-37-0	Butylated hydroxytoluene	23.4	Possibly Genotoxic
25395-31-7	Diacetin	5.9	Possibly Genotoxic
930-60-9	2-Cyclopentene-1,4-dione	5.0	Possibly Genotoxic
106-61-6	Glyceryl 1-acetate	4.0	Possibly Genotoxic
102-62-5	1,2-Diacylclycerol	2.4	Possibly Genotoxic
765-87-7	1,2-Cyclohexanedione	1.8	Possibly Genotoxic
28564-83-2	2,3-Dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one	1.6	Possibly Genotoxic
487-06-9	5,7-Dimethoxycoumarin	1.1	Possibly Genotoxic

Source: MR0000097, *"Tox-Ass-Report-NTDS-2017-fdafixed.pdf"*

IN VITRO STUDIES

The applicant submitted study reports for several in vitro cytotoxicity and mutagenicity assays for regular and menthol *HeatStick* aerosols and compared the results to reference cigarette smoke.

- Among these was the Ames test, which detects mutagenicity in bacteria.
- In the Ames test, reference cigarette total particulate matter (TPM; +S9) was mutagenic in 3 of the 5 bacterial strains, while *HeatStick* TPM was not mutagenic under any of the conditions tested.

IN VITRO STUDIES

The applicant submitted study reports for several in vitro cytotoxicity and mutagenicity assays for regular and menthol *HeatStick* aerosols and compared the results to reference cigarette smoke.

- While both reference cigarette smoke and *HeatStick* aerosols contains chemicals that are carcinogenic or possibly carcinogenic to humans (e.g., acetaldehyde, formaldehyde, benzene), *HeatStick* aerosols did not produce a positive response under conditions of the Ames test conducted by the applicant.
- The study reports did not contain information from an Ames test with the gas vapor phase (GVP) of the *HeatStick* aerosol. An Ames test with GVP would provide additional information about the mutagenic potential of *HeatStick* aerosol.

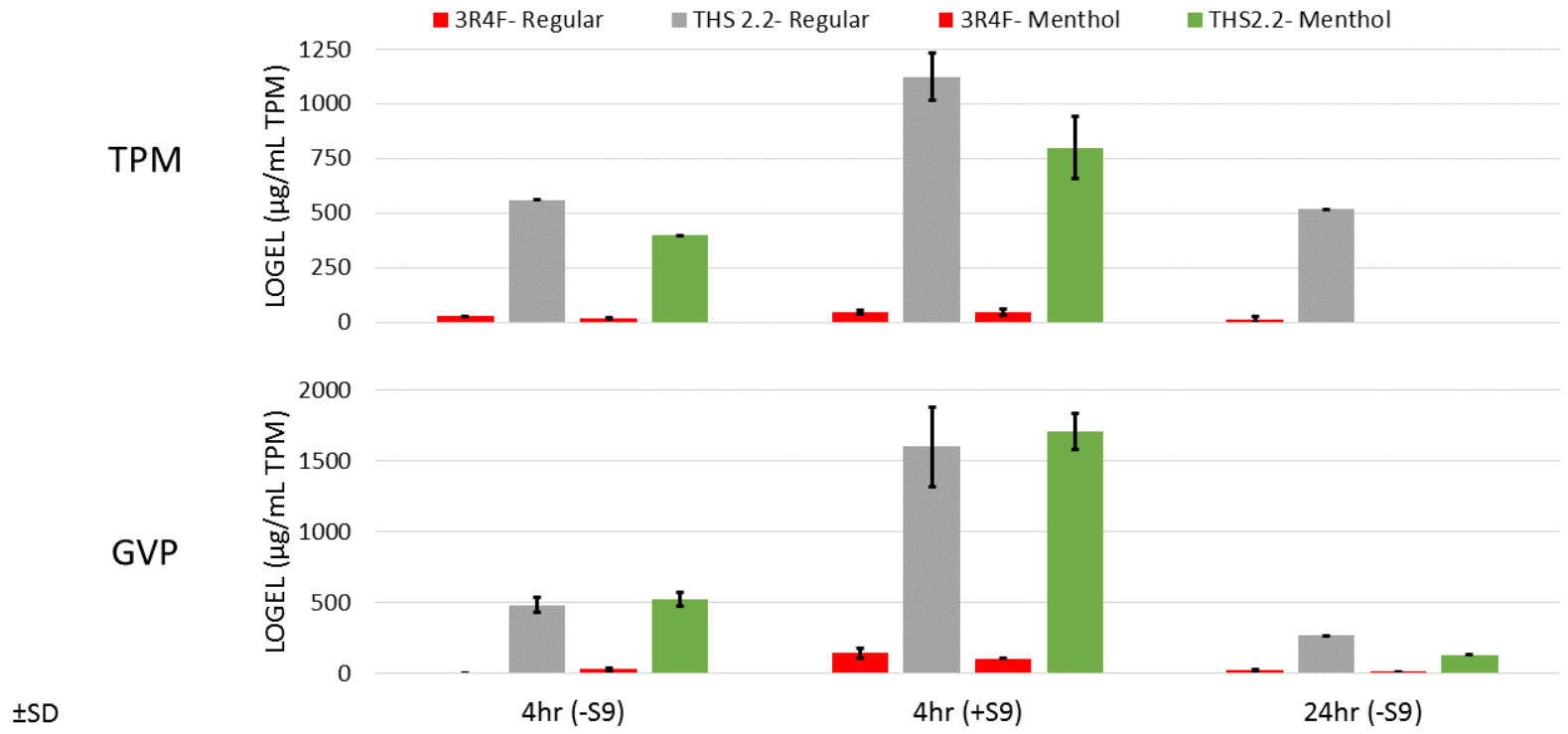
IN VITRO STUDIES

The applicant submitted study reports for several in vitro cytotoxicity and mutagenicity assays for regular and menthol *HeatStick* aerosols and compared the results to reference cigarette smoke.

- Study reports for neutral red uptake tests (NRU), which use a mammalian cell line to detect cytotoxicity, were also submitted.
- The NRU results indicate that *HeatStick* aerosols can be cytotoxic, but these effects are generally less severe and require higher levels of exposure than reference cigarette smoke.
- In the NRU test, total particulate matter (TPM) from *HeatStick* aerosols was 90% less cytotoxic than TPM from reference cigarette smoke.

IN VITRO STUDIES

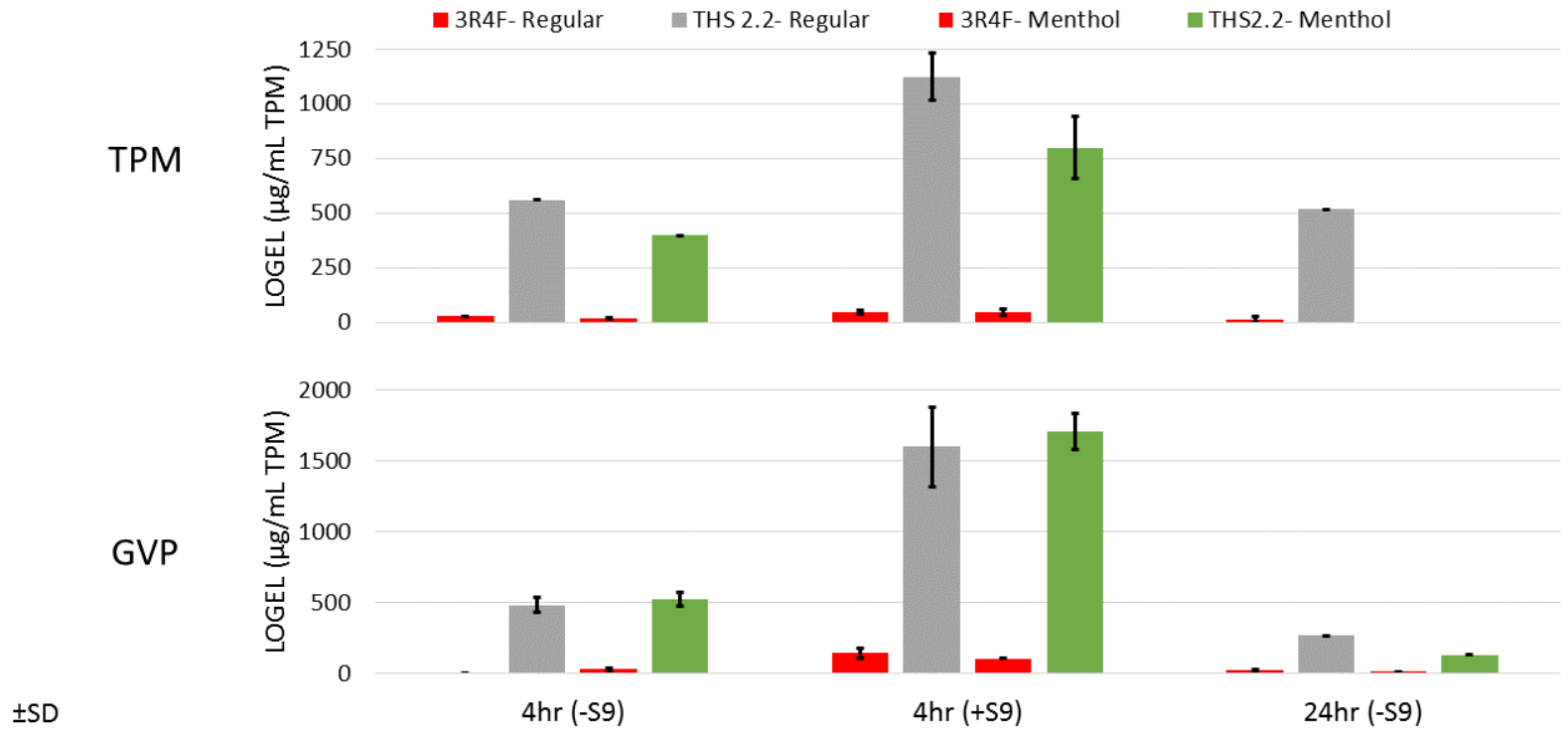
The applicant also submitted study reports from the mouse lymphoma assay (MLA), a test that detects mutagenicity in a mammalian cell line.



Source: Section 7.2, multiple files

IN VITRO STUDIES

HeatStick aerosols were mutagenic in the MLA, with toxicity occurring at higher concentrations compared to reference cigarette smoke. (↑15-30 fold for TPM, ↑8-24 fold for GVP).



Source: Section 7.2, multiple files

IN VITRO STUDIES

- The MLA study reports did ***not*** contain information about clastogenicity, or the capacity to cause damage to chromosomes.
- Also, while the MLA study, which is an in vitro test, indicates that *HeatStick* aerosols ***are*** mutagenic, there was no in vivo mutagenicity information which could have further clarified the mutagenic potential of the products.

Source: Section 7.2, multiple files

IN VITRO STUDIES

The applicant submitted data from five separate in vitro organotypic studies assessing the effects of aerosols from regular *HeatSticks* compared to reference cigarette smoke on human gingival, buccal, nasal, bronchial, and coronary arterial epithelium cultures.

- The results indicate that *HeatStick* aerosols generally produced fewer pathophysiological changes and adverse effects than reference cigarette smoke.
- For example, reference cigarette smoke produced significant cytotoxicity and histological changes in the bronchial epithelium that persisted for at least 72 hours, while *HeatStick* aerosols produced fewer effects, and those effects were less severe.

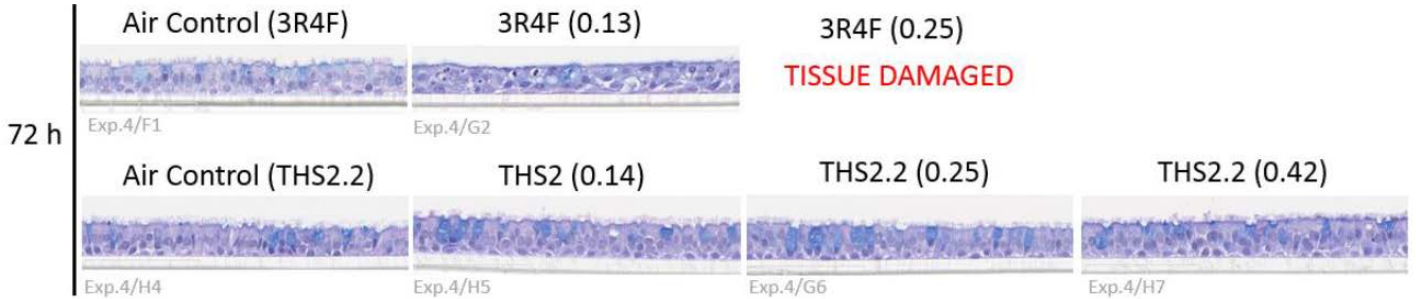


Image submitted by applicant in Section 7.5, "*1709_Organotypic_Bronch_SR.pdf*", Pg. 51, Fig. 3

IN VITRO STUDIES

- Similarly, *HeatStick* aerosols can have pro-inflammatory effects as well as adverse pathophysiological effects in buccal cell cultures, and alter responses to oxidative stress in gingival cell cultures, but those changes are less pronounced than effects from the 3R4F reference cigarette smoke and generally occur at higher concentrations.
- Also, *HeatStick* aerosols increased cell adhesion and reduced monocyte migration in coronary artery cell cultures, but only at higher concentrations than 3R4F reference cigarette smoke.

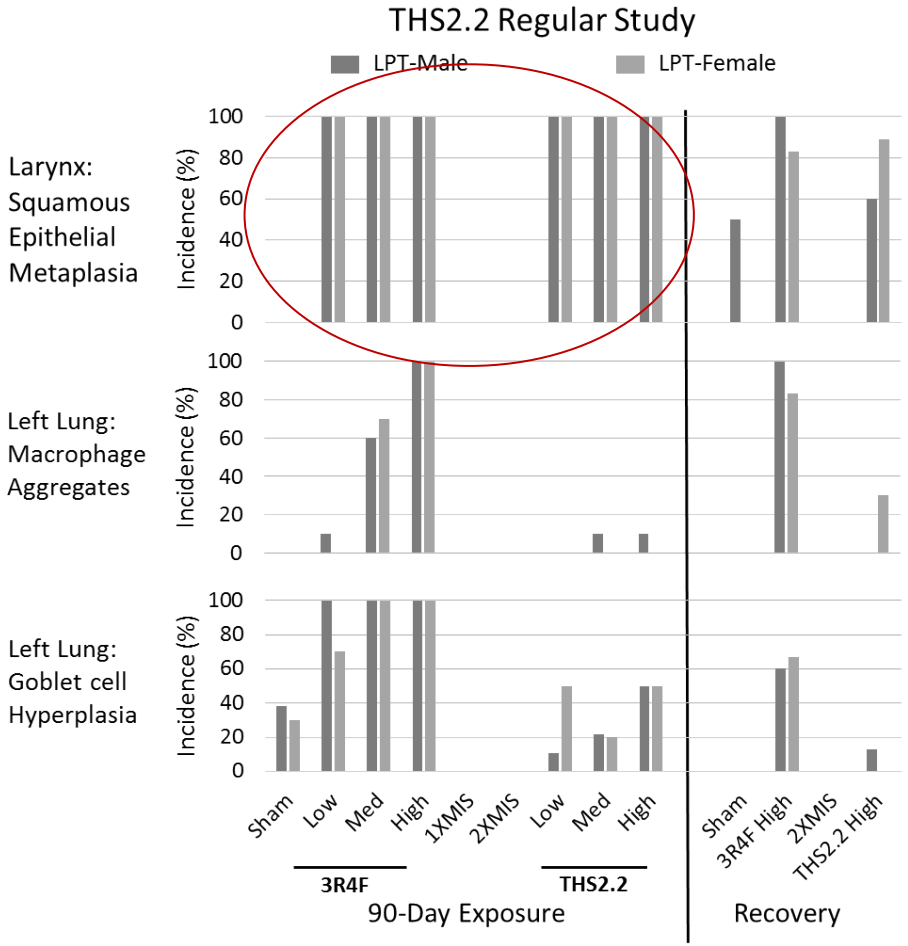
IN VIVO STUDIES

The applicant submitted study reports from two separate 90-day nose-only rat inhalation studies with a 42-day post-exposure recovery period using regular and menthol *HeatSticks,* as well as reference cigarettes.

- In general, repeated exposure to *HeatStick* aerosols produced fewer or less severe pathophysiological changes in the respiratory tract than exposure to reference cigarette smoke.
- However, some degeneration was observed in the larynx of rats exposed to either reference smoke or menthol *HeatStick* aerosols.
- Also, concentration-dependent increases in the epithelial thickness of the floor of the larynx and vocal cords occurred to a lesser extent in rats exposed to *HeatStick* aerosols than to those exposed to reference cigarette smoke.

IN VIVO STUDIES

For squamous metaplasia, a potentially precancerous lesion, the response produced in the larynx by *HeatStick* aerosols was similar to that of the reference cigarette smoke after the 90-day exposure period.



Source: Section 7.2, "*15006 THS SR Part 5.pdf*"

IN VIVO STUDIES

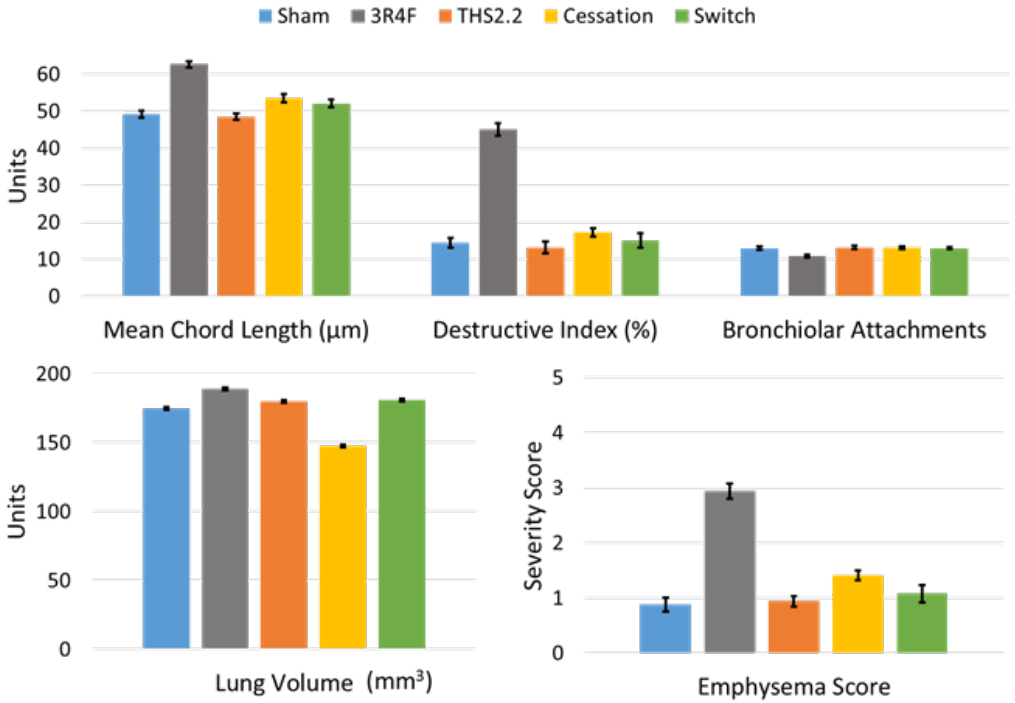
8-month Switching and Cessation Study with ApoE -/- Mice

- The ApoE-/- mouse model is well established for studying atherosclerosis, as mice develop hypercholesterolemia on a standard chow diet.
- Groups included:
  - Sham (filtered air for 8 months)
  - Reference cigarette smoke for 8 months
  - *HeatStick* aerosol for 8 months
  - Cessation (2 months reference cigarette smoke and 6 months filtered air)
  - Switching (2 months reference cigarette smoke and 6 months *HeatStick* aerosol)

IN VIVO STUDIES

8-month Switching and Cessation Study with ApoE -/- Mice

- Histopathological findings indicate that 8 months of reference cigarette smoke exposure increased mean cord length, destructive index, and alveolar emphysema score, and decreased the number of bronchiolar attachments compared to other groups.

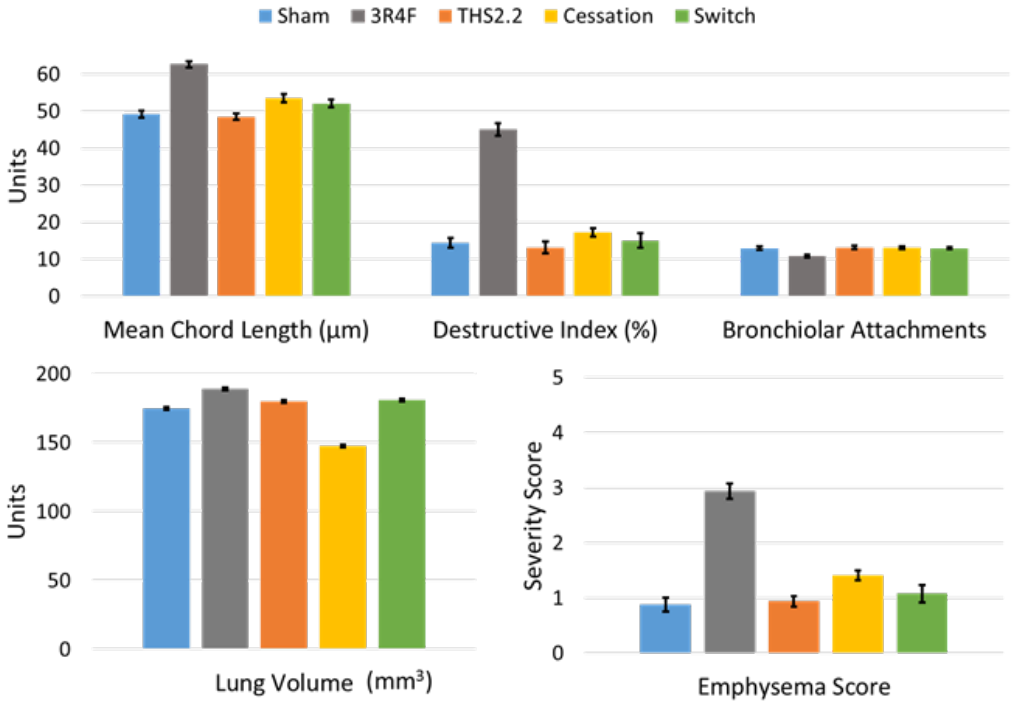


Source: Section 7.5, "*15015_CVD_Resp_ApoE_SW_SR_Part 5.pdf*"

IN VIVO STUDIES

8-month Switching and Cessation Study with ApoE -/- Mice

- Mice that were only exposed to the *HeatStick* aerosol, that switched from reference cigarette smoke to *HeatSticks* aerosol, that underwent cessation, and that were only exposed to sham conditions all had similar histopathological characteristics.

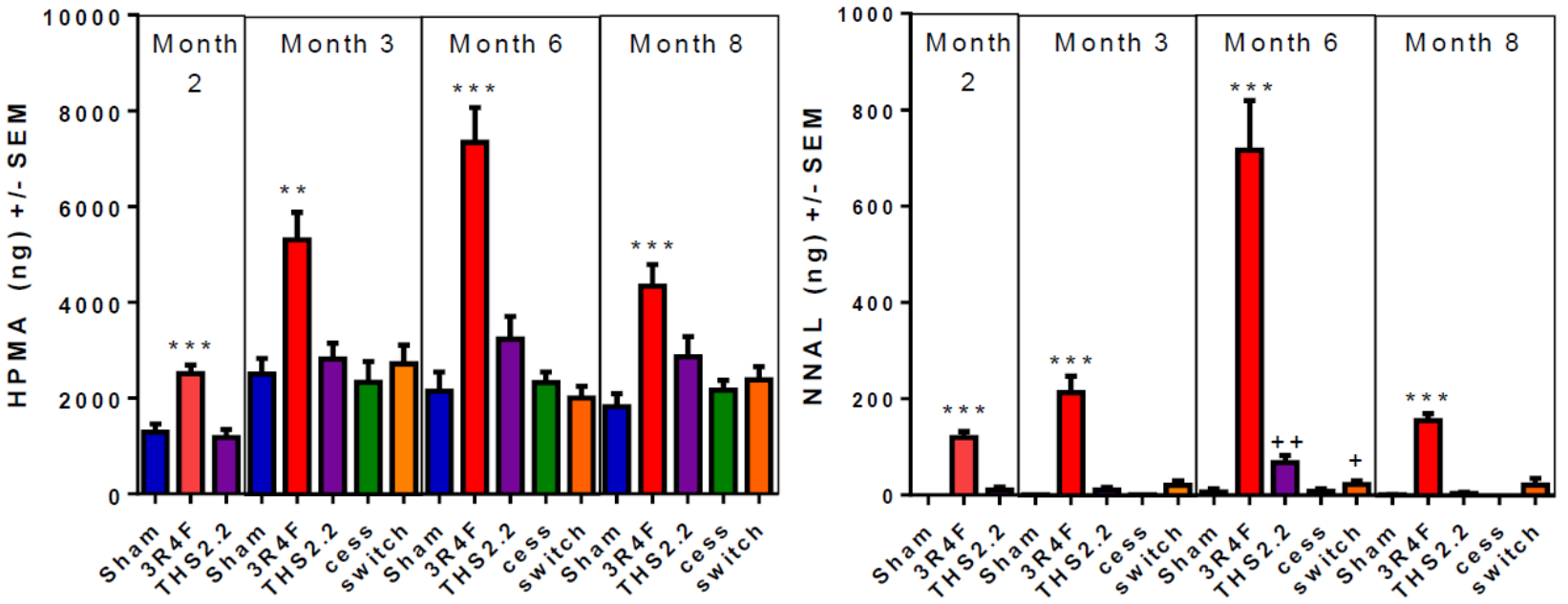


Source: Section 7.5, "*15015_CVD_Resp_ApoE_SW_SR_Part 5.pdf*"

IN VIVO STUDIES

8-month Switching and Cessation Study with ApoE -/- Mice

- Biomarkers of exposure for carbon monoxide, acrolein (shown), NNK (shown), benzene, and acrylonitrile, as well as some biomarkers of oxidative stress and inflammation were elevated in the ApoE -/- mice exposed to reference cigarette smoke, but not in the *HeatStick*-exposed or sham control mice.

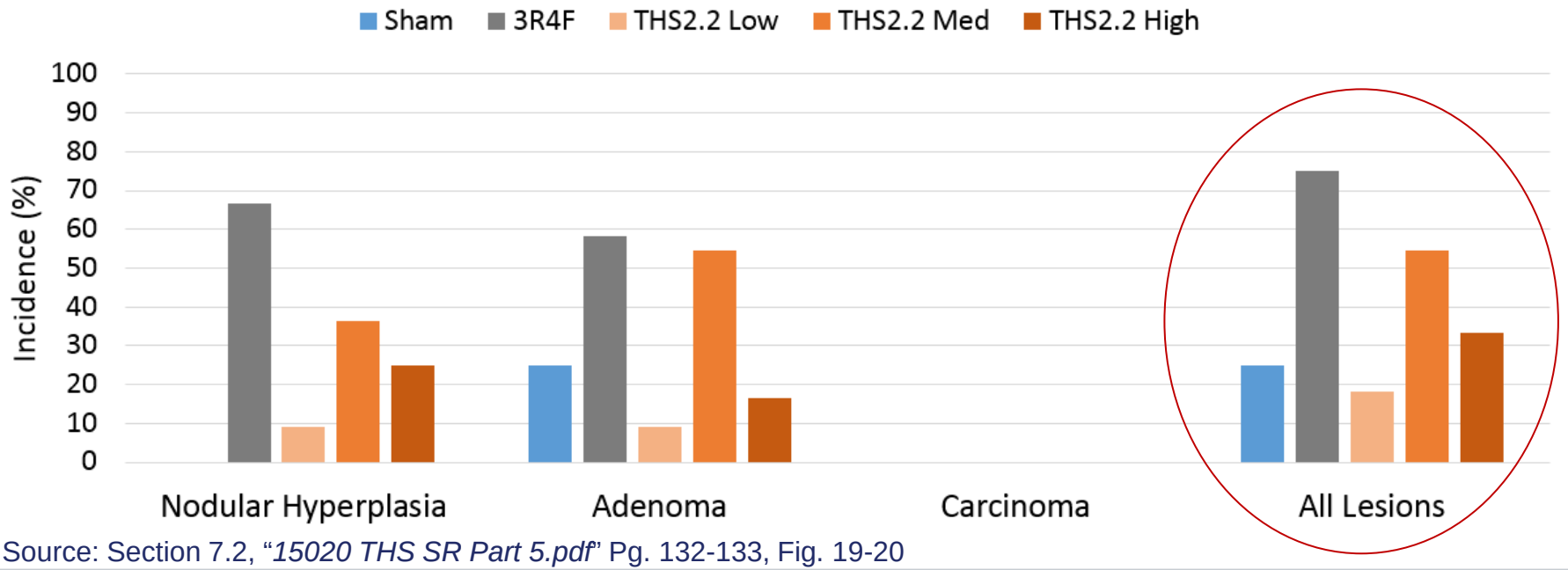


Source: Section 7.5, "*15015_CVD_Resp_ApoE_SW_SR_Part 1.pdf*"; Pg. 65, Fig. 12

RODENT CARCINOGENICITY STUDY

Preliminary data indicate that after 10 months of exposure, neoplastic lesions (e.g., bronchioloalveolar adenoma) were found in the lungs of female mice exposed to reference cigarette smoke and *HeatStick* aerosols.

- The study with male mice was terminated at 15 months due to a high number of deaths



Source: Section 7.2, "*15020 THS SR Part 5.pdf*" Pg. 132-133, Fig. 19-20

SUMMARY

- *HeatStick* aerosols demonstrated potential toxicity under the conditions tested by the applicant, but the adverse effects were generally fewer and less severe than what was observed with reference cigarette smoke.
- When *HeatStick* aerosols induced toxicity in the in vitro and in vivo studies, toxicity occurred at higher concentrations compared to reference cigarette smoke.
- *HeatStick* aerosols did not produce any additional adverse effects beyond those observed in test groups exposed to reference cigarette smoke.
- Based on the studies submitted, however, it is unclear if the effects observed in treatment groups exposed to *HeatStick* aerosols translate to a potential risk reduction for noncancer-related effects when chronically used by humans.

CLARIFYING QUESTIONS?