Hazard Identification and Cumulative Risk Assessment of NJOY® E-vapor Products

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September 15, 2025

Agenda

- Scientific Framework for New Tobacco Products
- NJOY® E-vapor Hazard Identification
- Chemical HGV/Dose Response Assessment
- Daily Exposure to NJOY® E-vapor Users
- NJOY® E-vapor Risk Characterization/QRA

HGV=Health-based guidance value. QRA= Quantitative risk assessment

FDA Regulation of Tobacco Products

Product Pathways

Premarket Tobacco Application (PMTA)

> …the finding as to whether the marketing of a tobacco product for which an application has been submitted is **appropriate for the protection of the public health (APPH)** shall be determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product…

Scientific Framework for New Tobacco Products

CONSTITUENT REDUCTION

Product Design and Control

Chemical and Physical Characterization

THE PRODUCT

- Chemistry Manufacturing and Controls
- Product Stability
- Chemical characterization

INDIVIDUAL RISK REDUCTION

Toxicology and Risk Assessment

Studies in Adult Human Subjects

EXPOSURE and HEALTH RISK

- Toxicology & Risk Assessment
- Health risk assessment (absolute and relative)
- Human Studies
- Human Factors Assessment

POPULATION HARM REDUCTION

Perception and Behavior Assessment

Risks and Benefits to Health of the Population

IMPACT on the POPULATION

- Risk perceptions (absolute and relative)
- Impact of product on users
- Impact on non-users
- Overall impact on the population
- Environmental Assessment

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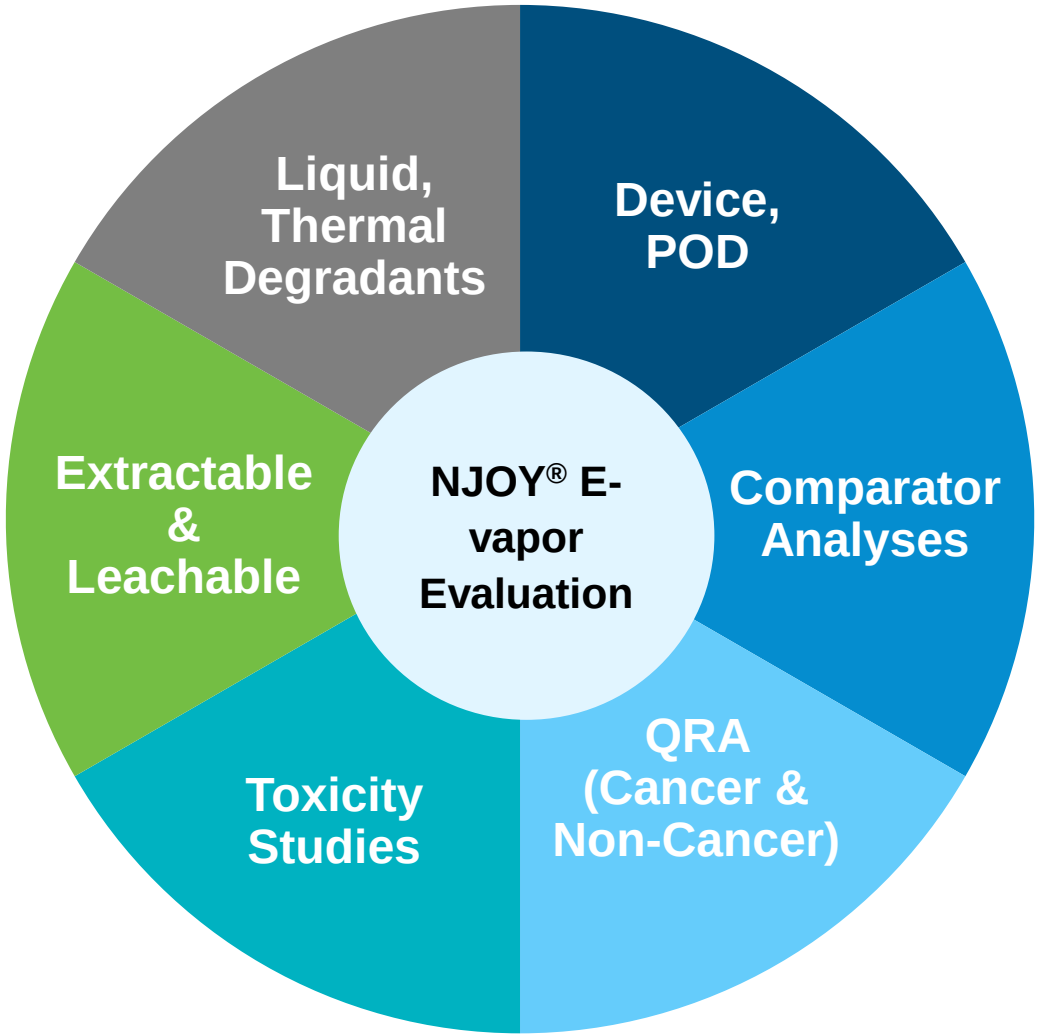
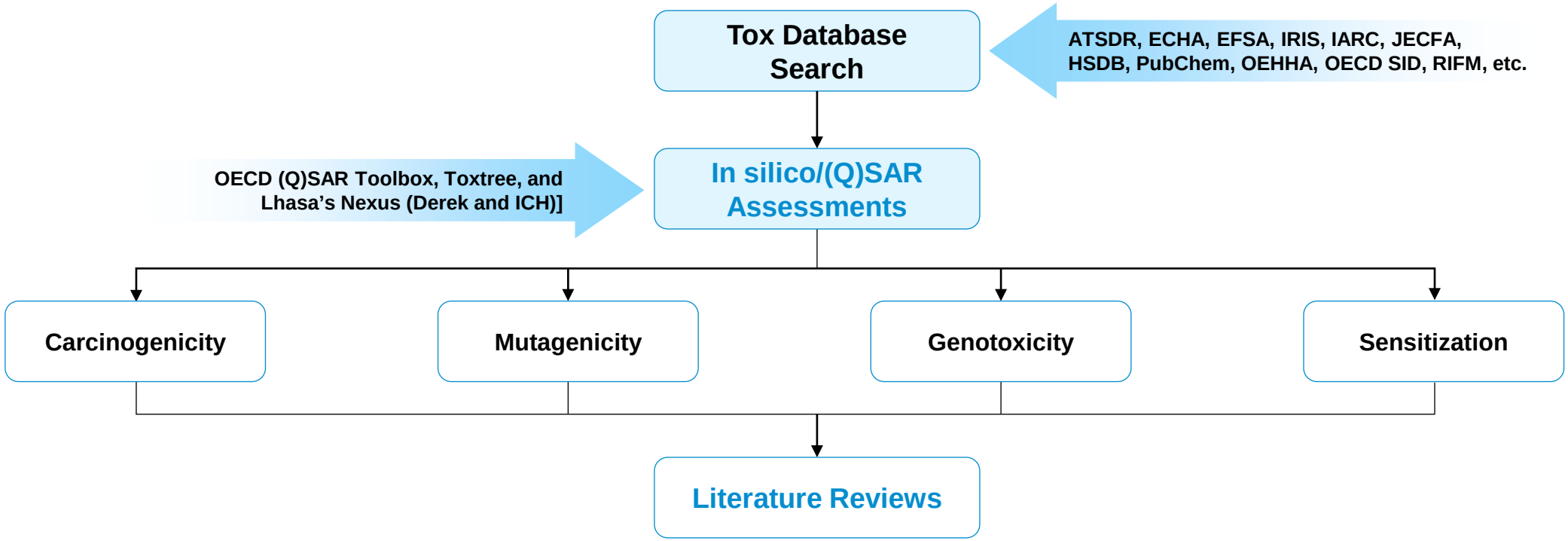
Individual Health Assessment: A Risk-based Approach



QRA=quantitative risk assessment; E-vapor Products=electronic nicotine delivery system.

Toxicological Assessment of Chemical Substances



- Literature reviews performed to verify QSAR-based predictions where possible
- Chemicals with positive experimental data in the publicly available literature were considered confirmed positive for CMRS, unless evidence from peer-reviewed literature suggested otherwise
- Final determinations for CMRS made based on a weight of evidence approach with empirical evidence having greater weight than computational modeling

ATSDR=Agency for Toxic Substances and Disease Registry; CMRs=carcinogenic, mutagenic, or reprotoxic substances; ECHA=European Chemicals Agency; EFSA=European Food Safety Authority; HSDB=hazardous substances data bank; IARC=International Agency for Research on Cancer; IRIS=Integrated Risk Information System; JECFA=Joint FAO/WHO Expert Committee on Food Additives; OECD SID=OECD Screening Information Dataset; OECD=Organisation for Economic Co-operation and Development; OEHHA=Office of Environmental Health Hazard Assessment; PubChem=open chemistry database (NIH); (Q)SAR=(quantitative) structure–activity relationship; RIFM=Research Institute for Fragrance Materials; TSDR=Agency for Toxic Substances and Disease Registry.

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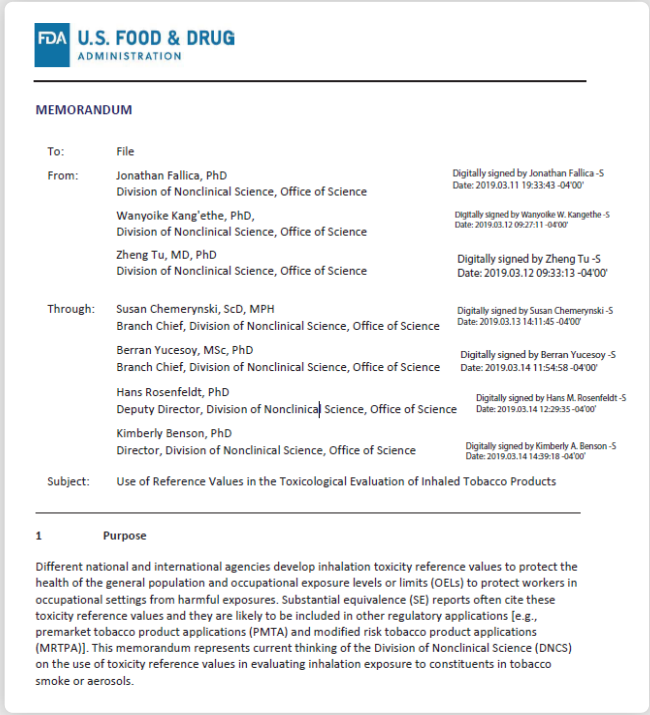
Health-based Guidance Values (HGVs)

Non-cancer and cancer endpoints

Tier-based Cancer and Non-cancer Health Guidance Value Selection

Priority	Agency	Values
Tier 1	EPA IRIS	RfC, IUR
Tier 2	EPA PPRTVs	RfC, IUR
Tier 3	ATSDR, EPA HEAST, TCEQ, TERA ITER, OEHHA, Health Canada, RIVM, FAO WHO JECFA, EFSA	MRL, RfC, ReV, IUR, ESL, MADL, NSRL, REL, IUR, TC, TCA/CR, ADI/TDI
Tier 4	ACGIH, NIOSH, OSHA, CA OSHA, AIHA, DFG, SCOEL, ECHA	TLV, REL, PEL, WEEL, MAK, TWA, DNEL/DMEL
Tier 5	Cramer, Barlow, Carthew, Escher	TTC



FDA U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM

To: File

From: Jonathan Fallica, PhD
Division of Nonclinical Science, Office of Science
Digitally signed by Jonathan Fallica -S Date: 2019.03.11 19:33:43 -04'00'

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Division of Nonclinical Science, Office of Science
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Zheng Tu, MD, PhD
Division of Nonclinical Science, Office of Science
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Through: Susan Chemerynski, ScD, MPH
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Deputy Director, Division of Nonclinical Science, Office of Science
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Kimberly Benson, PhD
Director, Division of Nonclinical Science, Office of Science
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Subject: Use of Reference Values in the Toxicological Evaluation of Inhaled Tobacco Products

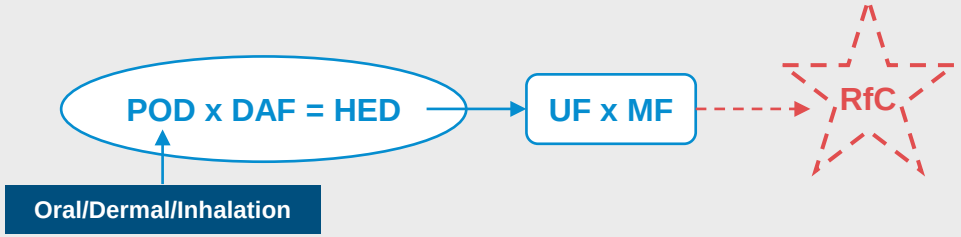
1 Purpose

Different national and international agencies develop inhalation toxicity reference values to protect the health of the general population and occupational exposure levels or limits (OELs) to protect workers in occupational settings from harmful exposures. Substantial equivalence (SE) reports often cite these toxicity reference values and they are likely to be included in other regulatory applications [e.g., premarket tobacco product applications (PMTA) and modified risk tobacco product applications (MRTPA)]. This memorandum represents current thinking of the Division of Nonclinical Science (DNCS) on the use of toxicity reference values in evaluating inhalation exposure to constituents in tobacco smoke or aerosols.

ACGIH=American Conference of Governmental Industrial Hygienists; ADI/TDI=acceptable daily intake / tolerable daily intake; AIHA=American Industrial Hygiene Association; ATSDR=Agency for Toxic Substances and Disease Registry; CA OSHA=California Occupational Safety and Health Administration; DFG=Deutsche Forschungsgemeinschaft; ECHA=European Chemicals Agency; EFSA=European Food Safety Authority; EPA HEAST=EPA Health Effects Assessment Summary Tables; EPA IRIS=EPA Integrated Risk Information System; EPA PPRTVs=EPA Provisional Peer-Reviewed Toxicity Values; EPA=Environmental Protection Agency; ESL=effects screening level; FAO=Food and Agriculture Organization; IUR=inhalation unit risk; JECFA=Joint FAO/WHO Expert Committee on Food Additives; MADL=maximally allowable dose level; MAK=maximum workplace concentration (Germany); MRL=minimal risk level; NIOSH=National Institute for Occupational Safety and Health; NSRL=no significant risk level; OEHHA=Office of Environmental Health Hazard Assessment; OSHA=Occupational Safety and Health Administration; PEL=permissible exposure limit; REL=recommended exposure limit; ReV=reference value; RfC=reference concentration; RIVM=Rijksinstituut voor Volksgezondheid en Milieu; SCOEL=Scientific Committee on Occupational Exposure Limits (European Commission); TC=tolerable concentration; TCA/CR=toxic concentration associated with cancer risk; TCEQ=Texas Commission on Environmental Quality; TERA=Toxicology Excellence for Risk Assessment; TLV=threshold limit value; TTC=threshold of toxicological concern; TWA=time-weighted average; WEEL=workplace environmental exposure level; WHO=World Health Organization. ITER= International Toxicity Estimates for Risk. DNEL=Derived No-Effect Levels. DMEL=Derived Minimal Effect Levels.

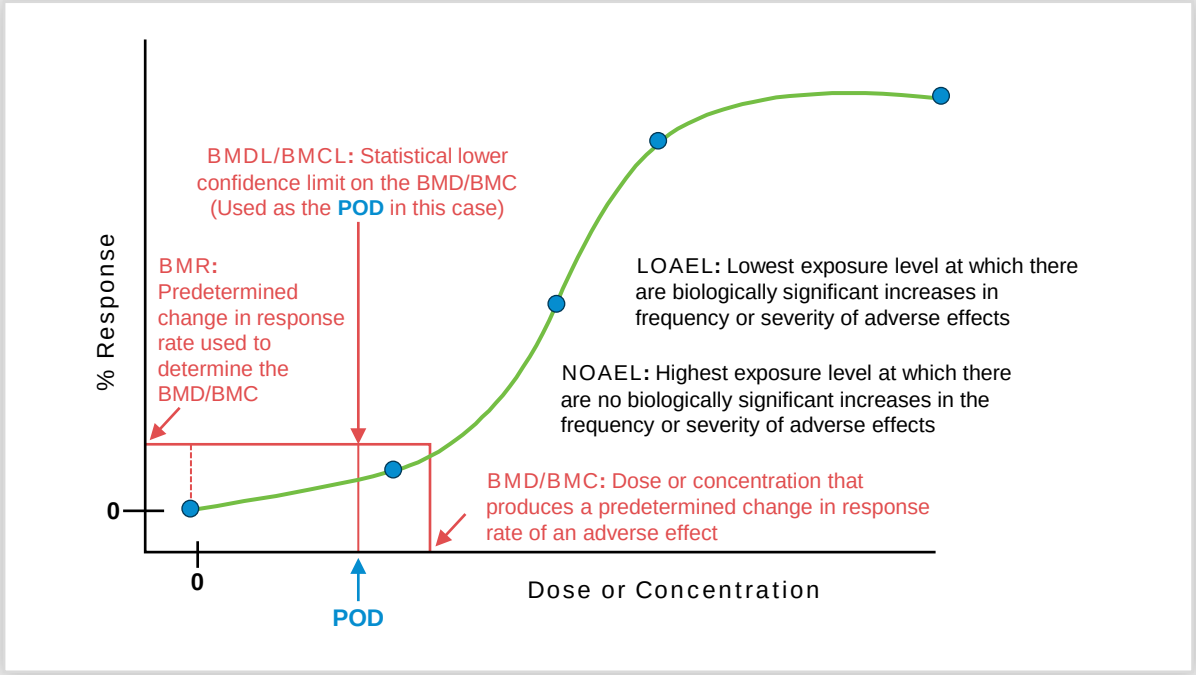
Reference Value Derivation

Using the POD (NOAEL, LOAEL, or BMDL) from peer reviewed toxicology studies



$$RfD\ or\ RfC = \frac{[NOAEL\ or\ LOAEL]}{\left[\prod_{i=1}^{n}(UF)_i \times MF\right]}$$

$$RfD\ or\ RfC = \frac{BMDL}{\left[\prod_{i=1}^{n}(UF)_i \times MF\right]}$$



POD= Point of Departure. NOAEL= No-Observed-Adverse-Effect Level. LOAEL= Lowest-Observed-Adverse-Effect Level. BMDL= Benchmark Dose Lower Confidence Limit. RfD=Reference Dose. RfC= Reference Concentration. HED= Human Equivalent Dose. UF=Uncertainty Factor. MF= Modification Factor

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Daily Exposure to NJOY® E-vapor Products Users

The exposure assessment considers the plausible range of puffs consumed in a day by typical and heavy users of NJOY® E-vapor Products

Multiple lines of evidence can support the estimate of puffs per day, including:

- PK and topography studies
- Consumer use surveillance studies, and
- Calculations of nicotine equivalent doses from other tobacco products, such as combustible cigarettes

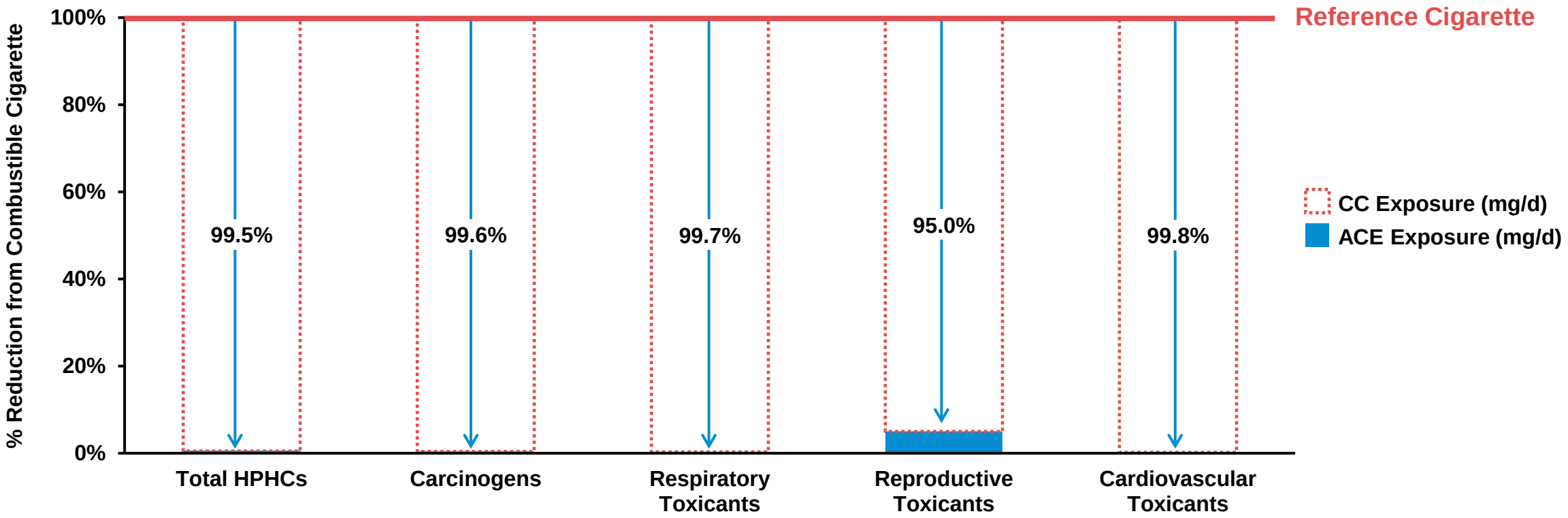
Daily Exposure (mg/day) = C x M x P

C=Concentration in e-liquid (%)
M=Aerosol mass per puff (mg/puff)
P=Puff# per day to achieve equivalent nicotine dose for typical and heavy users

E-vapor Products=electronic nicotine delivery system; PK=pharmacokinetics.

Comparator Analysis: NJOY® E-vapor Products vs. CC

Estimated exposure to harmful constituents from NJOY® E-vapor products by endpoints were substantially reduced compared to CC



The comparison of the aerosol levels of harmful constituents between NJOY® E-vapor Products and CC is consistent with the in vitro assay results

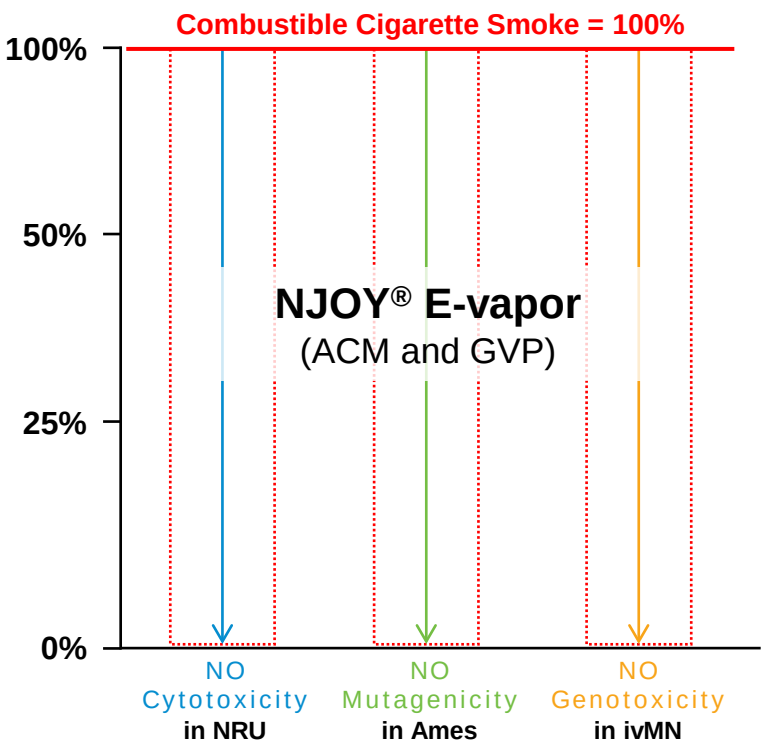
CC=combustible cigarette; E-vapor Products=electronic nicotine delivery system; HPHC=harmful and potentially harmful constituents.

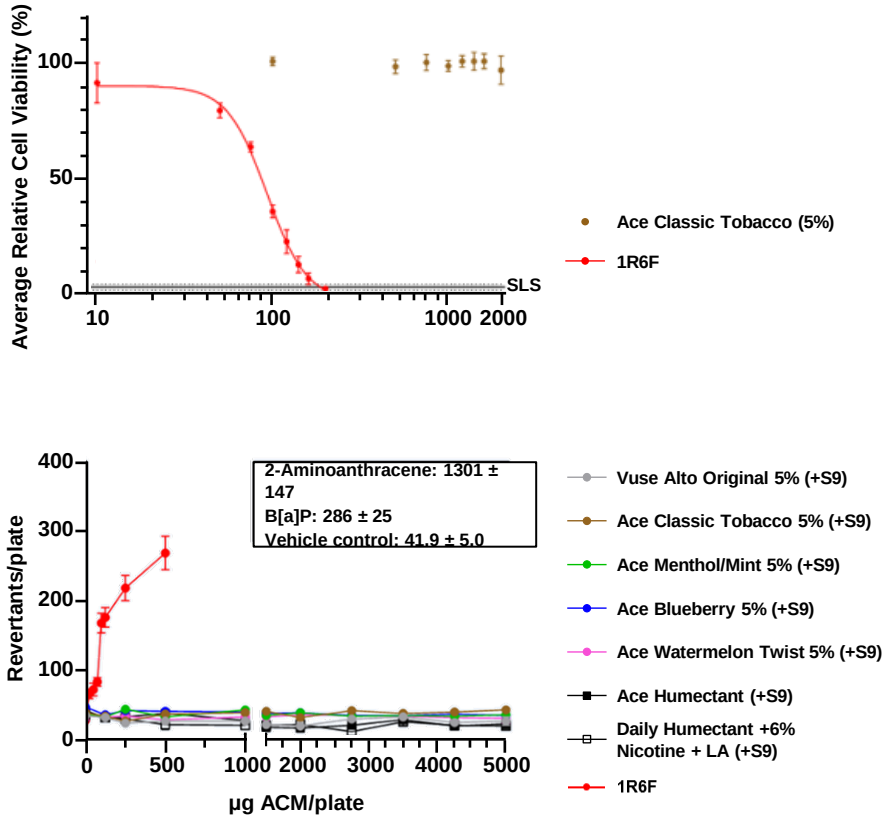
NJOY® E-vapor Product *In Vitro* Effects

CONSTITUENT REDUCTION

Studies on the finished products provided a solid understanding of the relative risks of the aerosol mixture in comparison to CC

NJOY® E-vapor mainstream aerosol collected matter (ACM) and gas vapor phase (GVP) substantially less cytotoxic, mutagenic and genotoxic compared to cigarette smoke

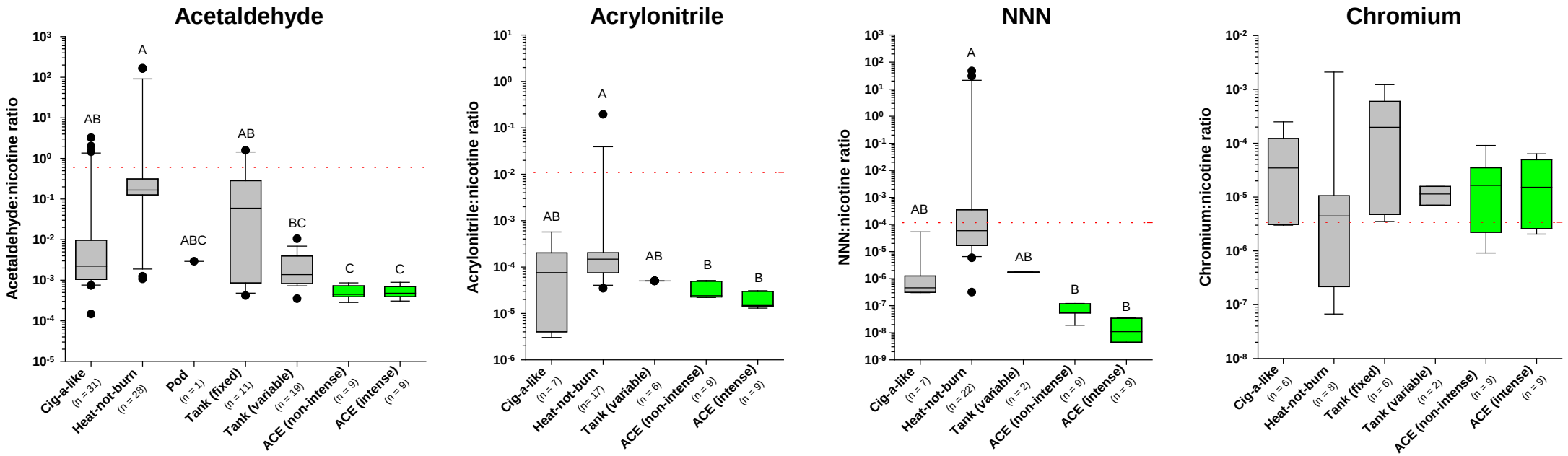




1R6F=16RF reference cigarette; ACM=Aerosol collected matter; CC=Combustible cigarette; EVAP=E-vapor products; GVP=Gas vapor phase; NRU=Neutral Red Uptake; Ames=Ames test; ivMN=*in vitro* micronucleus.

Comparator Analysis: NJOY® E-vapor Products vs. Other E-vapor Products

NJOY® E-vapor Products consistently demonstrated HPHCs* **(e.g., carbonyls, VOCs, and TSNAs)** less than or similar exposures to other products, **including HNB, cig-a-likes, tanks, and PODS**



*The 95th Percentile of NJOY E-vapor Products aerosol concentration vs. the average aerosol concentration data from peer-reviewed scientific literature representing other E-vapor Products category (nicotine-adjusted)
E-vapor Products=electronic nicotine delivery system; HNB=heat-not-burn products; HPHC=harmful and potentially harmful constituents; NNN=N-nitrosonornicotine; TSNAs=tobacco-specific nitrosamines; VOCs=volatile organic compounds.

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NJOY® E-vapor Product Risk Characterization vs. CC

The cumulative non-cancer (for respiratory endpoints) and cancer risks from exposure to HPHCs are substantially lower than CC

NON-CANCER RISK REDUCTION **of HPHCs Compared to CC**

HPHCs	ACE vs. CC (% Lower)
Carbonyls	95.9-99.9%
VOCs	90.4-99.8%
Cadmium and Lead	98.7-99.5%
…	…
Cumulative Risk of Respiratory Effects[1]	93-95%

[1] If propylene glycol is not considered

CANCER RISK REDUCTION **of HPHCs Compared to CC**

HPHCs	ACE vs. CC (% Lower)
Carbonyls	95.9-99.9%
VOCs	90.4-99.8%
TSNAs	99.9%
Cadmium and Lead	98.7-99.5%
…	…
Cumulative Risk[2]	98%

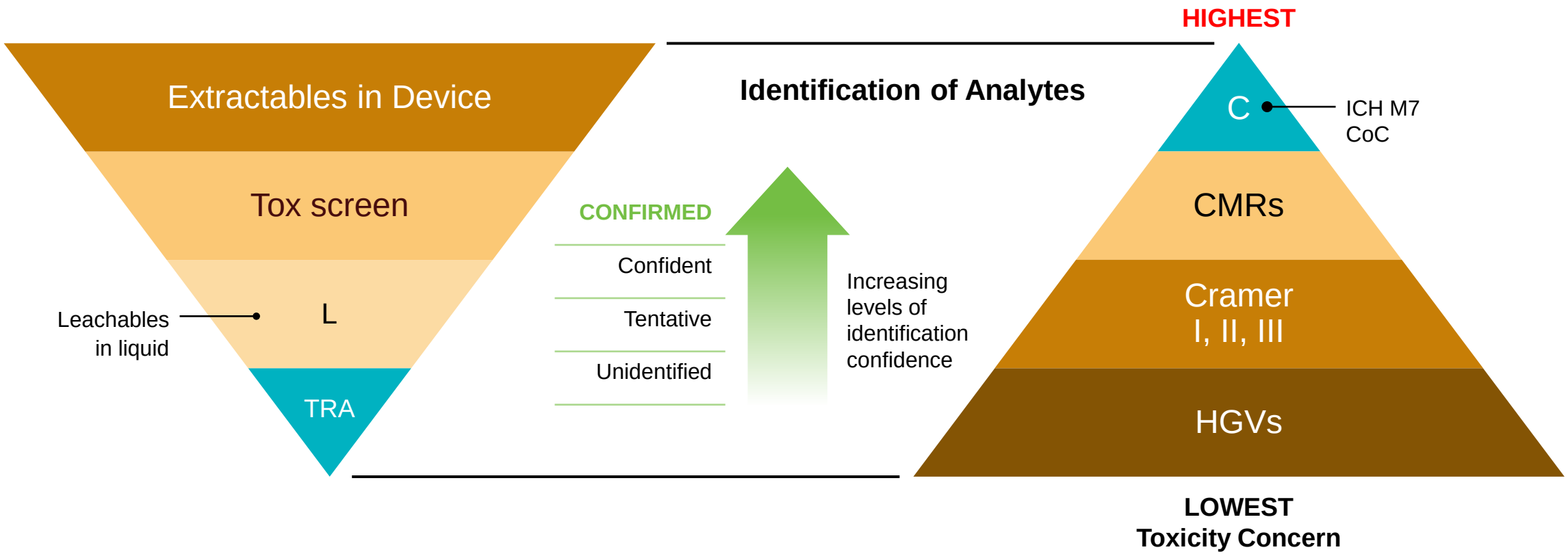
[2] If glycidol is not considered

Examples of the health risk of NJOY® E-vapor Products compared to CC under non-intense puffing and ambient storage conditions

CC=combustible cigarette; E-vapor Products=electronic nicotine delivery system; HPHC=harmful and potentially harmful constituents; TSNAs=tobacco-specific nitrosamines; VOCs=volatile organic compounds.

Extractables and Leachables

Leachable compounds were below 25%–50%
of the HGVs at all stability time points



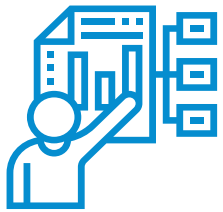
PQRI Guidance, ISO 10993 – 1/17/18, and ICH Q3, M7
C=control; CMRs=carcinogenic, mutagenic, or reprotoxic substances; CoC=class of concern; HGVs=health guidance values; ICH M7 = International Council for Harmonization, Guideline M7; L=leachables; TRA=toxicological risk assessment.

A Pragmatic and Holistic Approach Developed to Evaluate NJOY® E-vapor Products

This is a risk-based approach contemplating:

- **Hazard analysis** (of the liquid, POD, and device),
- **Consumer exposure** to the hazardous constituents,
- **Comparative product analysis**, and
- **QRA**

The application of the methodology demonstrates that as an alternative to CC, **the NJOY® E-vapor Products demonstrates a significantly reduced toxicological risk**



THE APPROACH HAS BEEN SUCCESSFUL IN ACHIEVING

MARKET GRANTING ORDERS (MGOS) FOR NJOY® E-VAPOR PRODUCTS

CC=combustible cigarette; E-vapor Products=electronic nicotine delivery system; PMTA=premarket tobacco application; QRA=quantitative risk assessment.

Conclusion – TPL Review

“ Based on the information provided in the PMTAs and the available evidence, I find that permitting the marketing of the new products in accordance with the requirements in the marketing granted orders is appropriate for the protection of the public health (APPH).”

“Chemical evaluation of the new NJOY products’ aerosols suggests that the new products have fewer, and lower levels of many HPHCs compared to CC.”

“The applicant has therefore demonstrated the potential for these products to benefit adult smokers who switch completely or significantly reduce their cigarette consumption as compared those who continue to use CC exclusively.”

“The toxicology review concludes the new products have lower noncancer risk, compared to CC, and that the new products’ ELCRc is significantly lower than the ELCRc in adults who smoke CC.”

Marketing Granted Order

June 21, 2024

April 26, 2022

CC=combustible cigarette; ELCRc=calculated excess lifetime cancer risk; HPHC=harmful and potentially harmful constituents; PMTA=premarket tobacco application. TPL=Technical Project Lead.

Acknowledgements

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