# Nicotine, Menthol, and Melanin: A Deadly Combo for Black Americans

Dr. Valerie Yerger
Professor in Health Policy
University of California, San Francisco

April 26, 2024

## DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH THE TOBACCO INDUSTRY

Nothing to disclose

## DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH PHARMACEUTICALS OR INSTRUMENTS

Own distributorship in a nutritional supplement company

# Learning Objectives

Discuss relationships between nicotine, melanin, and menthol

Explore possible intersectionality between stress, nicotine dependence, and skin color

DOCUMENTS

PHILIP MORRIS

BROWN & WILLIAMSON TOBACCO

RJReynolds

Lorillard

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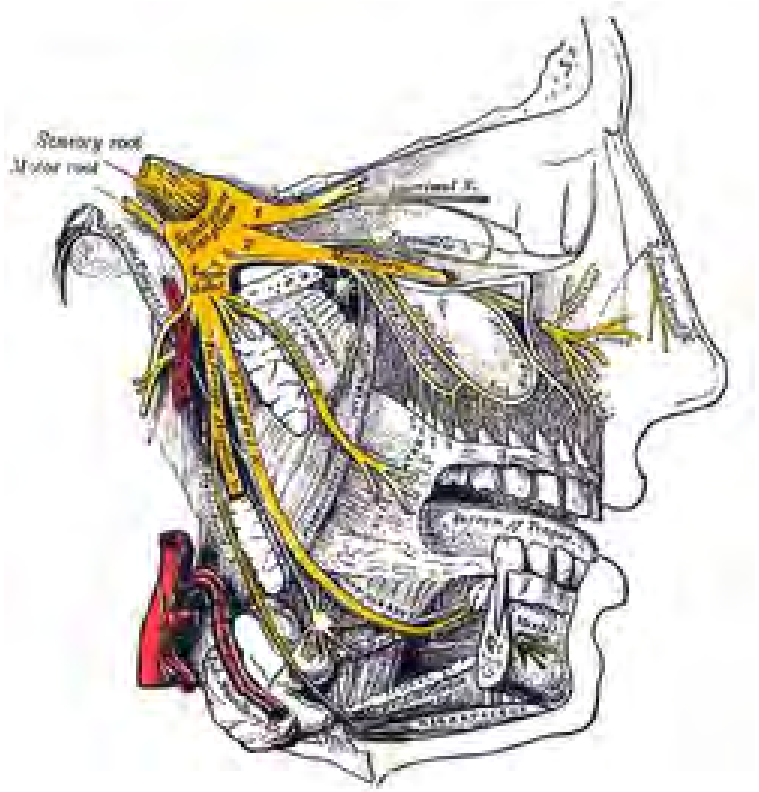
# Nicotine and Menthol

# Menthol Stimulates the Trigeminal Nerve



Trigeminal is the 5th cranial nerve, widely distributed throughout the head

Of interest to the tobacco industry because nicotine also stimulates this nerve

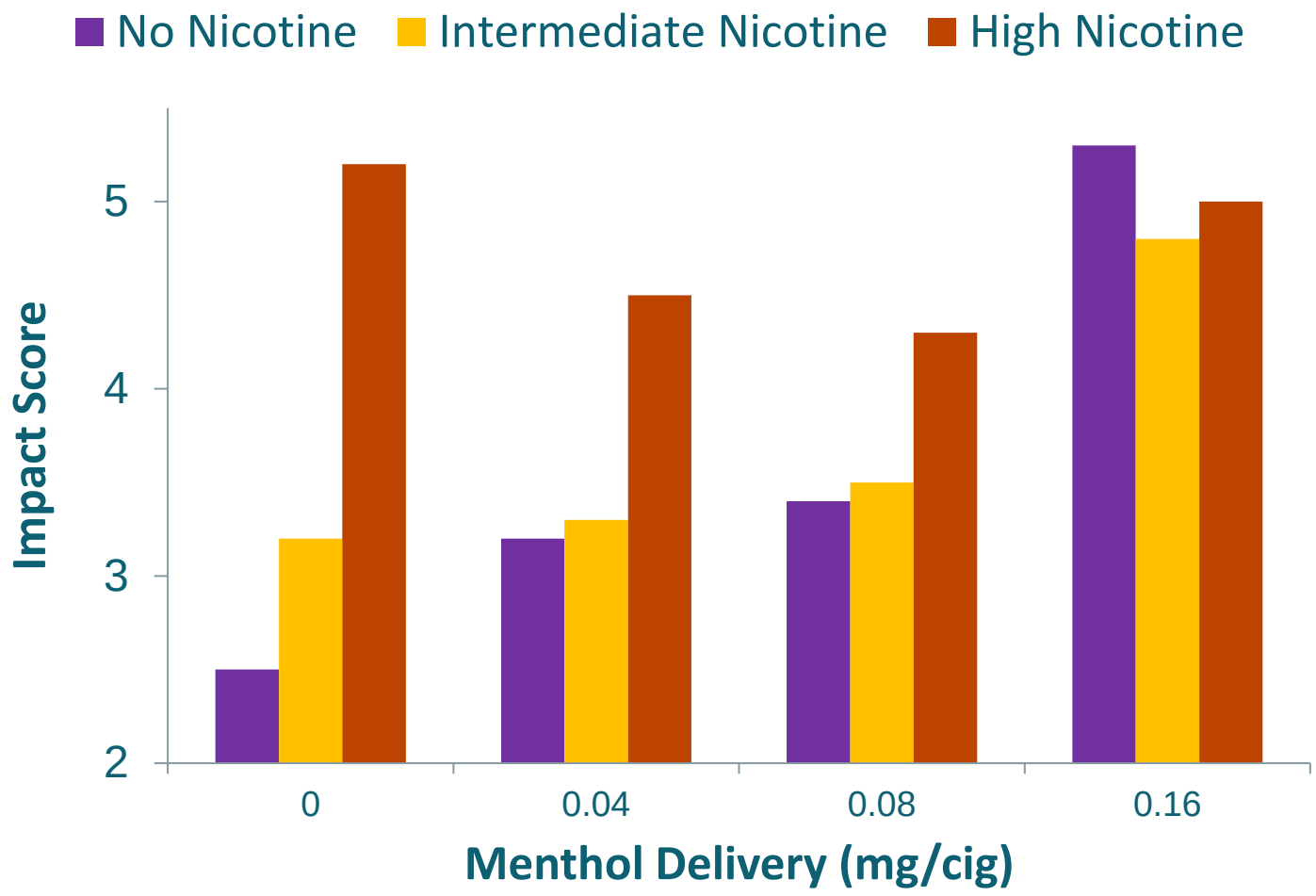
Essential to eliciting a liking response for a tobacco product

Menthol found to be a “partial replacement” for nicotine (Philip Morris, 1990)

Yerger VB (2011). Menthol's potential effects on nicotine dependence: A tobacco industry perspective. Tobacco Control, 20 Suppl 2:ii29-36.

# Menthol Modulates Nicotine's Effects

Philip Morris in-house study, 1991

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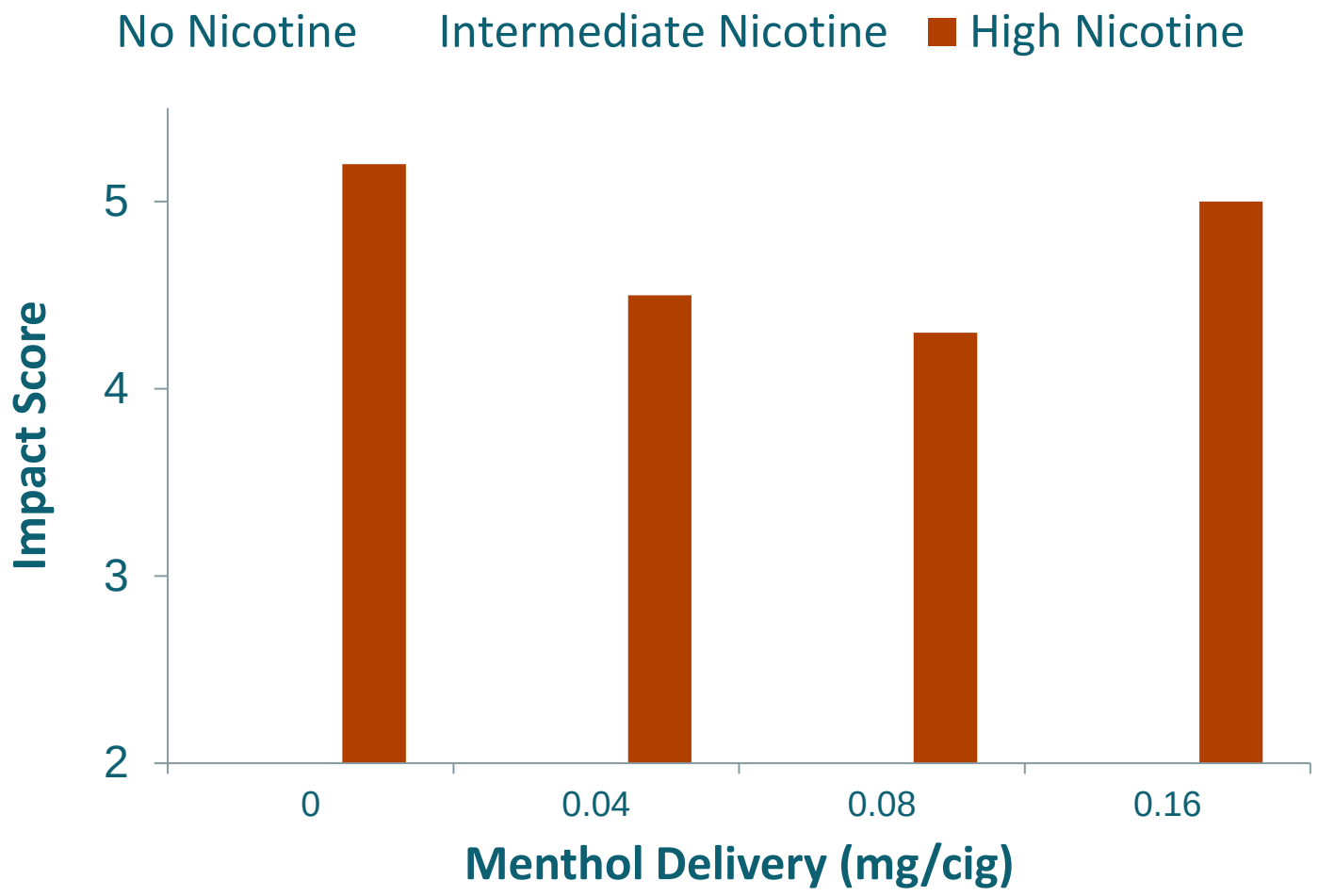


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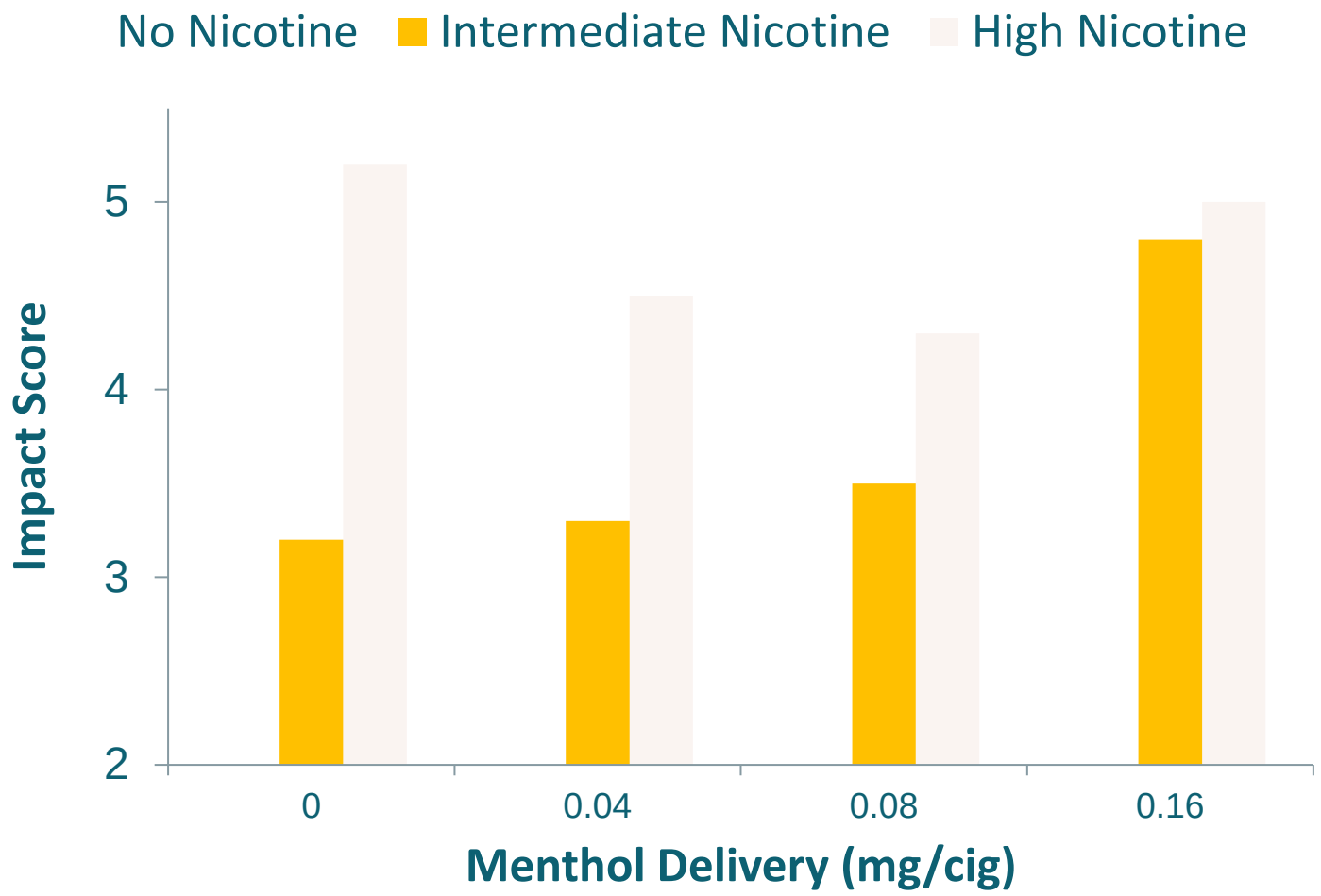


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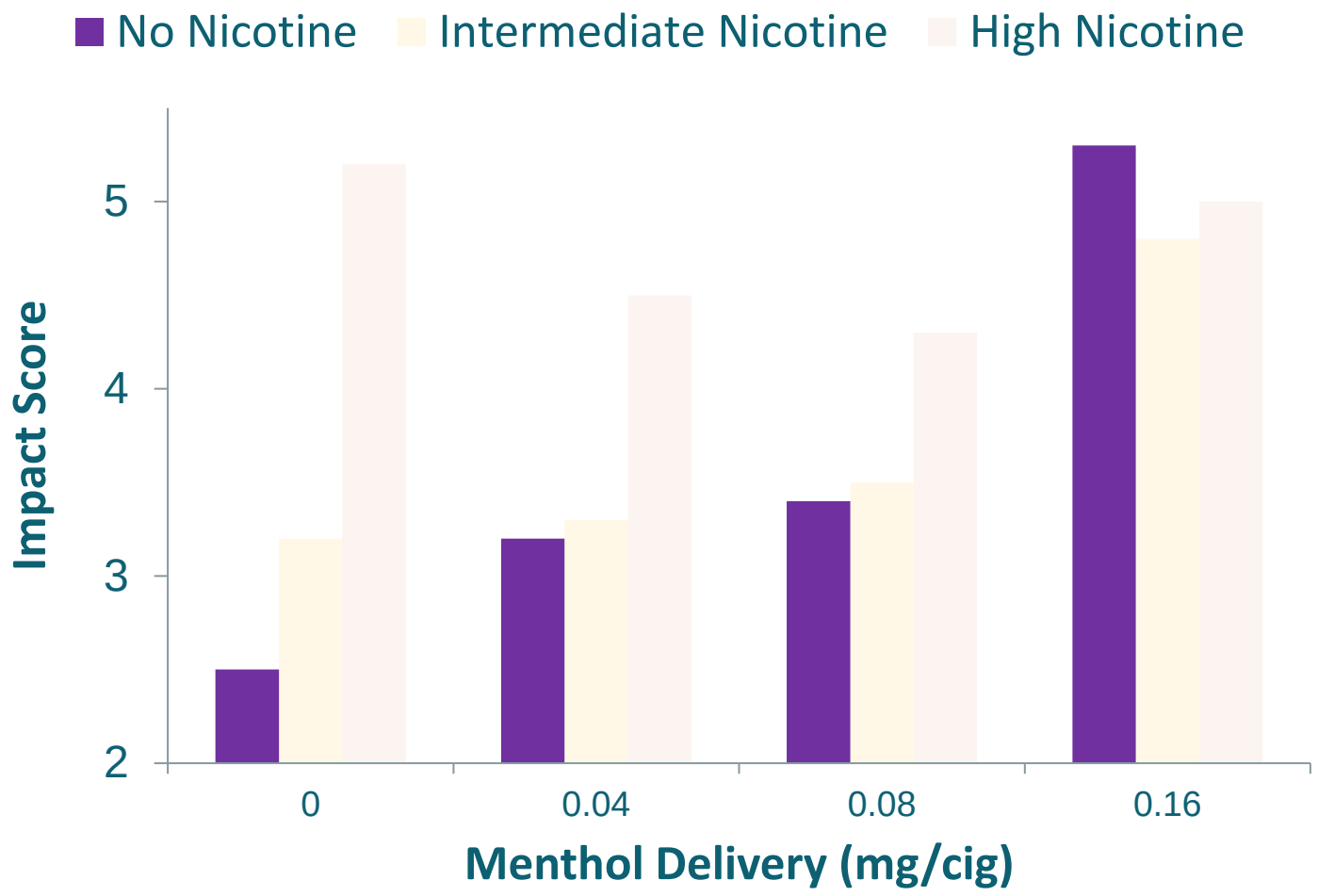


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# Nicotine and Melanin

# NICOTINE & MELANIN
# LINKED TO TOBACCO DEPENDENCE?

**Ethnic Differences in Cotinine Levels**

Black American smokers have highest levels of cotinine, despite lower cigs/day (CPD)

Studies reported that Black Americans metabolize cotinine significantly slower than Whites

Slower metabolism may indicate a greater level of dependence, more difficulty quitting, and greater exposure to cigarette toxins and carcinogens

“Black smokers appear to take in and absorb more nicotine than White smokers”

Wagenknecht et al, 1990; Caraballo et al., 1998; Perez-Stable et al., 1998

# Melanin Linked to Tobacco Dependence?

# MELANIN LINKED TO NICOTINE DEPENDENCE?

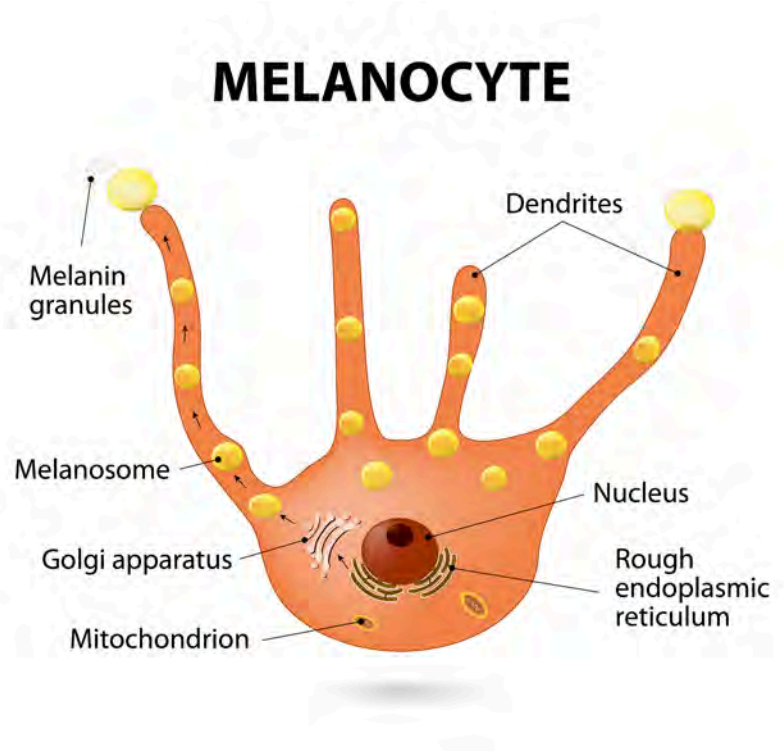
**Melanin**

Pigment that gives color to the skin, eyes, and hair

Synthesized solely by melanocytes in the basal layer of the epidermis

Skin coloration is adaptive human trait and adjusts to environmental conditions

Also located in the heart, lungs, brain lymphocytes, and inner ear



# Melanin: Constitutive vs. Facultative

Constitutive melanin – no significant associations between avg number of cigs smoked per day (CPD), time to first cigarette (TTFC), or cotinine concentration

Facultative melanin – significantly and positively related to CPD, TTFC, and cotinine

Greater tanning potential (difference between facultative melanin and constitutive melanin) is associated with greater nicotine use and dependence

King, Yerger, et al., 2009. Link between facultative melanin and tobacco use among African Americans. *Pharmacology, Biochemistry and Behavior*, 92 (2009), 589-596.)

CARDIOVASCULAR, PHARMACOLOGY and CHEMISTRY

#382

COMMITTEE:
Dr. Jacobson, CHM.
Dr. Cattell
Dr. Bing

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 EAST FORTY SECOND STREET NEW YORK 17, N. Y.

## Application For Research Grant

Date: FEBRUARY 8, 1963

1. Name of Investigator: CARL G. SCHMITERLOW, M.D., PH.D.

Studies on the uptake, distribution and metabolism in the brain are scarce. We intend to emphasize on the following:

1) Anatomical and cellular localization of nicotine in the brain after different routes of administration.
2) Further studies on the metabolism of nicotine in the brain.
2) a) After removal of the liver, intestine and kidneys.
b) In vitro metabolism of nicotine by brain slices.
3) Distribution in autonomic ganglia.

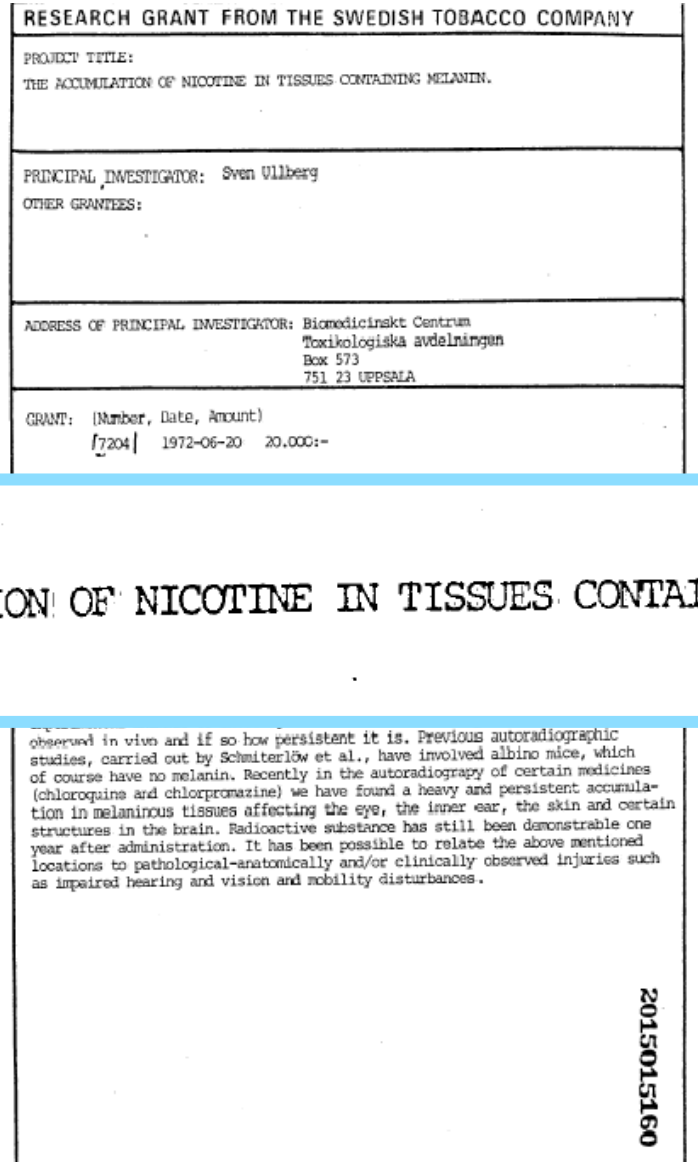
Technique: $C^{14}$-labeled nicotine will be prepared as earlier described (Schmiterlöw & Hansson, Nature 194, 298, 1962, Hansson & Schmiterlöw, J. Pharm. and Exper. Ther. 137, 91, 1962, Appelgren, Hansson & Schmiterlöw, Acta Physiol. Scand. 56, 249, 1962) by methylating nornicotine. The distribution of nicotine in the brains will be studied on sections of the whole brain and on a cellular level with the use of microautoradiographic techniques. Both techniques are developed in our laboratory. The metabolic state of nicotine in the brain will be investigated with standard chemical methods.
The distribution of nicotine in ganglia will be studied with microautoradiographic methods developed in our laboratory (see list of Publications from our department).

Some of our results have been presented for the TIRC of one member of our staff (Dr E. Hansson) on the 28th of September at the Round Table Discussion "Effects of nicotine on the central nervous system". He is now on a visit in U.S.A. but will return next year and work on this project.

# MELANIN LINKED TO NICOTINE DEPENDENCE?

**Tobacco Industry Research**

Swedish Tobacco Company, 1972



RESEARCH GRANT FROM THE SWEDISH TOBACCO COMPANY

PROJECT TITLE:
THE ACCUMULATION OF NICOTINE IN TISSUES CONTAINING MELANIN.

PRINCIPAL INVESTIGATOR: Sven Ullberg
OTHER GRANTEES:

ADDRESS OF PRINCIPAL INVESTIGATOR: Biomedicinskt Centrum
Toxikologiska avdelningen
Box 573
751 23 UPPSALA

GRANT: (Number, Date, Amount)
[7204] 1972-06-20 20.000:-

observed in vivo and if so how persistent it is. Previous autoradiographic studies, carried out by Schmiterlöw et al., have involved albino mice, which of course have no melanin. Recently in the autoradiograpy of certain medicines (chloroquins and chlorpromazine) we have found a heavy and persistent accumulation in melaninous tissues affecting the eye, the inner ear, the skin and certain structures in the brain. Radioactive substance has still been demonstrable one year after administration. It has been possible to relate the above mentioned locations to pathological-anatomically and/or clinically observed injuries such as impaired hearing and vision and mobility disturbances.

2015015160

PROJECT TITLE:

THE ACCUMULATION OF NICOTINE IN TISSUES CONTAINING MELANIN.

# MELANIN LINKED TO NICOTINE DEPENDENCE?

found. However, the fortuitous inclusion of both pigmented and albino strains revealed a remarkable affinity of nicotine for melanin. Also, the use of

## WHOLE-BODY AUTORADIOGRAPHIC STUDIES OF THE DISTRIBUTION AND METABOLISM OF NICOTINE-$^{14}C$

*William J. Waddell, Ph.D., and Carolyn Marlowe*

*Department of Pharmacology*
*College of Medicine*
*University of Kentucky*
*Lexington, Kentucky*

pigmented strains, radioactivity was also concentrated in melanin. The metabolites, cotinine-$^{14}C$ and nicotine-1′-N-oxide-$^{14}C$, did not localize in respiratory epithelia. Lung tissue that had been frozen before incubation with nicotine-$^{14}C$ or cotinine-$^{14}C$ did not accumulate radioactivity in the bronchial epithelium. Pretreatment with cysteamine or progesterone *in vivo* decreased the localization of radioactivity in bronchi after administration of nicotine-$^{14}C$; but pretreatment with SKF 525A, piperonyl butoxide, $NaHCO_3$ or $NH_4Cl$ had no effect on this accumulation of radioactivity. The experiments suggest that nicotine is concentrated in respiratory epithelium because it is actively metabolized in these cells.

The distribution of nicotine-$^{14}C$ was studied by whole-body autoradiography in three different strains of mice with different sensitivities to the

prior to the nicotine-$^{14}C$ in an attempt to dissect the mechanism of accumulation. In addition, sections and lungs from mice that had received no treatment were incubated *in vitro* with nicotine-$^{14}C$ under a variety of conditions. The binding to melanin appears to be a simple affinity of a basic compound to an acidic protein. The localization in bronchial epithelium appears to be associated with metabolic conversion in these cells.

### Materials and Methods

#### *in vivo* Studies

Adult male and female mice, weighing 20-25 g and pregnant mice, weighing 25-35 g of the C57BL/6J, C57L/J, and A/HeJ strains were obtained from Jackson Laboratories, Bar Harbor,

# MELANIN LINKED TO NICOTINE DEPENDENCE?

and one albino -- markedly different in their susceptibility to the lethal effects of tobacco smoke and nicotine. An immediate and intense localization of radioactivity was seen in melanin in the eye, skin and meninges of the frontal cortex in the two pigmented strains. An equally rapid and in-

April 22, 1974

MEMORANDUM

TO: W. T. Hoyt

CC: HHR RCH
WTH WK
WUG

FROM: Leonard S. Zahn

SUBJECT: Federation of American Societies for Experimental Biology, Atlantic City, N.J., April 7-12, 1974

have stories in the weeks ahead; many of these journals had reporters covering the meeting, the world's largest in terms of number of papers presented.

Smoking was mentioned numerous times in an almost incidental manner, in papers and press conferences on such subjects as atherosclerosis, viruses, carcinogenesis, etc.

Some highlights:

1. "Histopathology of respiratory system of Bio 15.16 hamsters chronically exposed to cigarette smoke" -- Freddie Homburger, Cambridge, Mass. A news release on Homburger's report was placed in the press room the day he gave his paper. It was one-page to which was attached a "corrected copy" of the paper he presented at the 1973 meeting of the Society of Toxicology.

The release described research on Bio 15.16 and 87.20 hamster strains and said larynx cancer, "which in man has been linked to smoking," has been produced in Syrian golden hamsters exposed to cigarette smoke for 80-90 weeks. It went on to say: "20% of the histologically examined larynxes showed early carcinoma, indistinguishable from the microscopic appearance of such lesions in patients. In about half of the animals, after 45 or more weeks of smoking, the laryngeal lining near the vocal cords showed changes ranging from simple thickening to leukoplakia and pseudoepitheliomatous hyperplasia. This corresponds to human 'smoker's larynx' often seen in heavy smokers and drinkers and believed to lead to cancer of the larynx. Some of the larynxes with epithelial hyperplasia taken from animals that had smoked for nearly two years were transplanted into cheek pouches of young hamsters where they survived for as long as one year without further smoking. The epithelial changes induced by smoking persisted in some of these transplants."

In actual presentation of his paper, Homburger opened

Leonard Zahn and Associates, Inc. PUBLIC RELATIONS COUNSEL

# NICOTINE BINDS TO MELANIN

Nicotine either binds directly to melanin or becomes entrapped inside the melanocyte during melanin synthesis

Once nicotine enters a melanocyte, it then enters the melanosome and interacts with melanosomal proteins

Nicotine accepted as a precursor during the formation of new melanin. Structural resemblance between nicotine and melanin's precursor Indole-5,6-quinone

Yerger VB and Malone RE (2006). Melanin and nicotine: A review of the literature. *Nicotine and Tobacco Research.* 8: 487-497.

# NICOTINE ACCUMULATION IN MELANIN

Nicotine has been shown to be retained in melanin-containing tissues for up to 30 days after a single intravenous injection (Lindquist & Ullberg, 1974)

Other studies also found accumulation and long-term retention of nicotine in melanin-containing structures (Barza et al. 1979; Lindquist & Ullberg, 1975; Mizuno, et al. 1997)

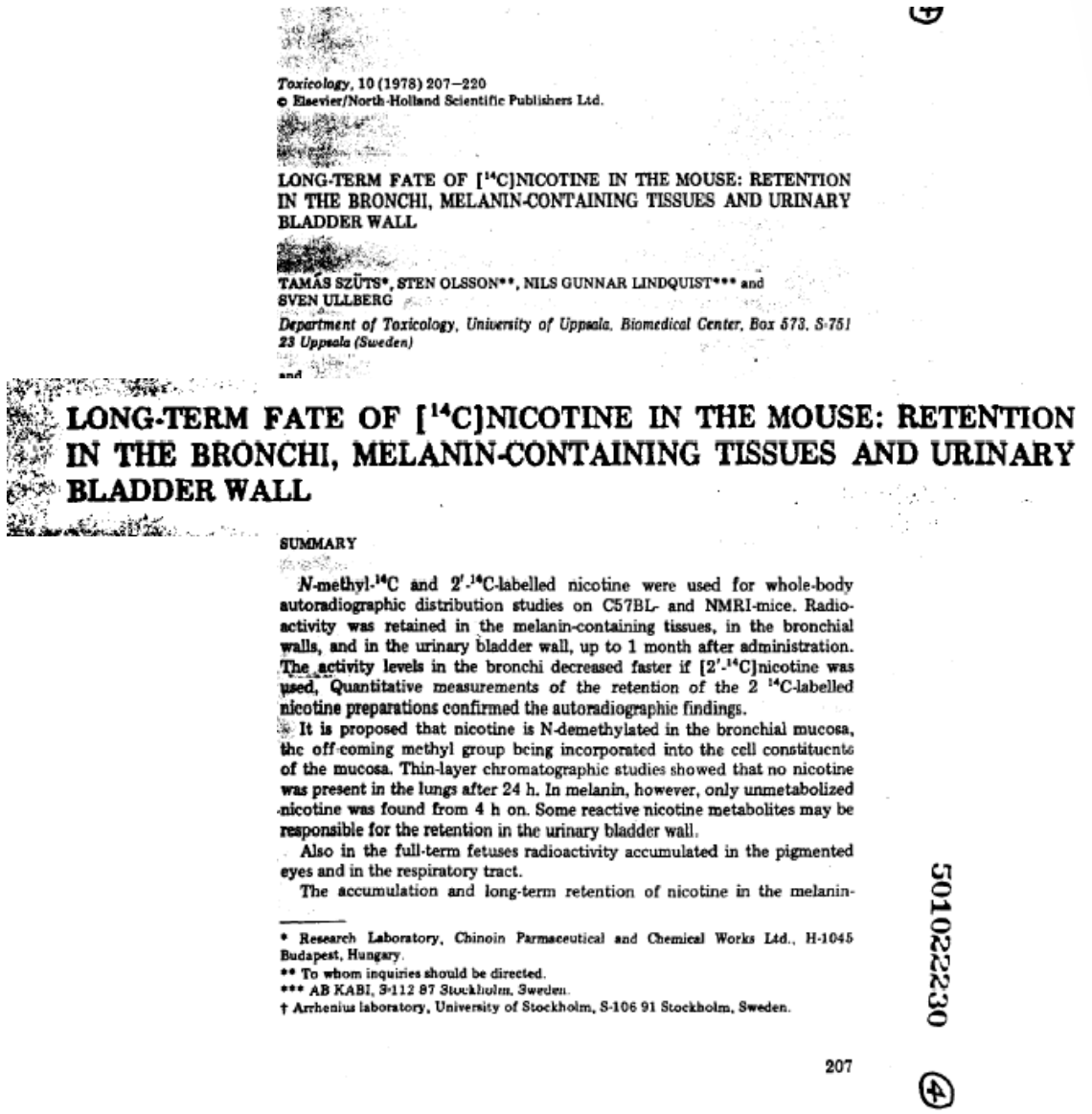
Tobacco specific carcinogens also bind to melanin, including most potent and abundant nitrosonomicotine (NNN)

Yerger VB and Malone RE (2006). Melanin and nicotine: A review of the literature. *Nicotine and Tobacco Research.* 8: 487-497.

# MELANIN LINKED TO NICOTINE DEPENDENCE?

*[A]ccumulation and long-term retention of nicotine in the melanin-containing structures might accelerate the development of drug-induced or senile changes in these tissues.*

*Swedish Tobacco Company Research (1978)*



Toxicology, 10 (1978) 207–220
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LONG-TERM FATE OF [$^{14}$C]NICOTINE IN THE MOUSE: RETENTION IN THE BRONCHI, MELANIN-CONTAINING TISSUES AND URINARY BLADDER WALL

TAMÁS SZÜTS*, STEN OLSSON**, NILS GUNNAR LINDQUIST*** and SVEN ULLBERG

*Department of Toxicology, University of Uppsala, Biomedical Center, Box 573, S-751 23 Uppsala (Sweden)*

and

LONG-TERM FATE OF [$^{14}$C]NICOTINE IN THE MOUSE: RETENTION IN THE BRONCHI, MELANIN-CONTAINING TISSUES AND URINARY BLADDER WALL

SUMMARY

*N*-methyl-$^{14}$C and 2′-$^{14}$C-labelled nicotine were used for whole-body autoradiographic distribution studies on C57BL- and NMRI-mice. Radioactivity was retained in the melanin-containing tissues, in the bronchial walls, and in the urinary bladder wall, up to 1 month after administration. The activity levels in the bronchi decreased faster if [2′-$^{14}$C]nicotine was used. Quantitative measurements of the retention of the 2 $^{14}$C-labelled nicotine preparations confirmed the autoradiographic findings.

It is proposed that nicotine is N-demethylated in the bronchial mucosa, the off-coming methyl group being incorporated into the cell constituents of the mucosa. Thin-layer chromatographic studies showed that no nicotine was present in the lungs after 24 h. In melanin, however, only unmetabolized nicotine was found from 4 h on. Some reactive nicotine metabolites may be responsible for the retention in the urinary bladder wall.

Also in the full-term fetuses radioactivity accumulated in the pigmented eyes and in the respiratory tract.

The accumulation and long-term retention of nicotine in the melanin-

* Research Laboratory, Chinoin Parmaceutical and Chemical Works Ltd., H-1045 Budapest, Hungary.
** To whom inquiries should be directed.
*** AB KABI, S-112 87 Stockholm, Sweden.
† Arrhenius laboratory, University of Stockholm, S-106 91 Stockholm, Sweden.

# MELANIN LINKED TO NICOTINE DEPENDENCE?

*Nicotine & Tobacco Research* Volume 8, Number 4 (August 2006) 487–498

Taylor & Francis
Taylor & Francis Group

**Review**

## Melanin and nicotine: A review of the literature

**Valerie B. Yerger, Ruth E. Malone**

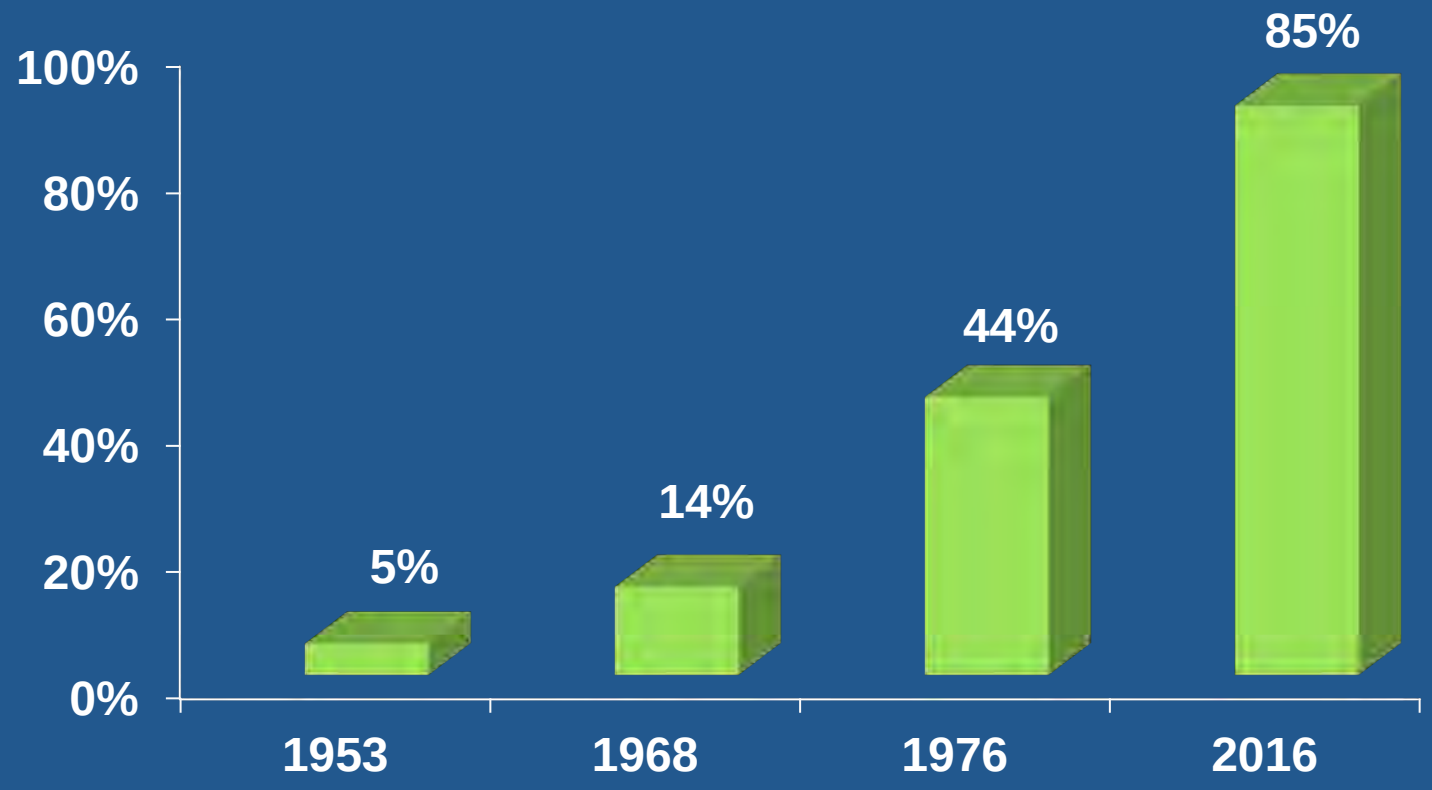
# MELANIN LINKED TO NICOTINE DEPENDENCE?

*The higher amounts of melanin in African Americans may contribute to higher nicotine dependence and lower tobacco quit rates, which then lead to poorer health outcomes.*

Yerger VB & Malone RE (2006). Melanin and nicotine: A review of the literature. Nicotine and Tobacco Research, 8(4), 487-498.

# Menthol and Melanin

# Menthol Use Among Adult African American Smokers




Sources: 1) Gardiner PS. The African Americanization of menthol cigarette use in the United States. *Nicotine Tob Res 2004;6 suppl 1:S55-65.* 2) Lorillard, 1986; TID: ybv44a00; Giovino et al 2016.

# Young Adult Blacks: “The Trendsetters”

“Trends are often started by low income males…The daring, flamboyant aspect of [young adult] black smokers’ personalities are evident in the many trends they start…these trends often spread to the general population…

RJR, 1989; TID: wug34d00

# Latino Smokers and Menthol

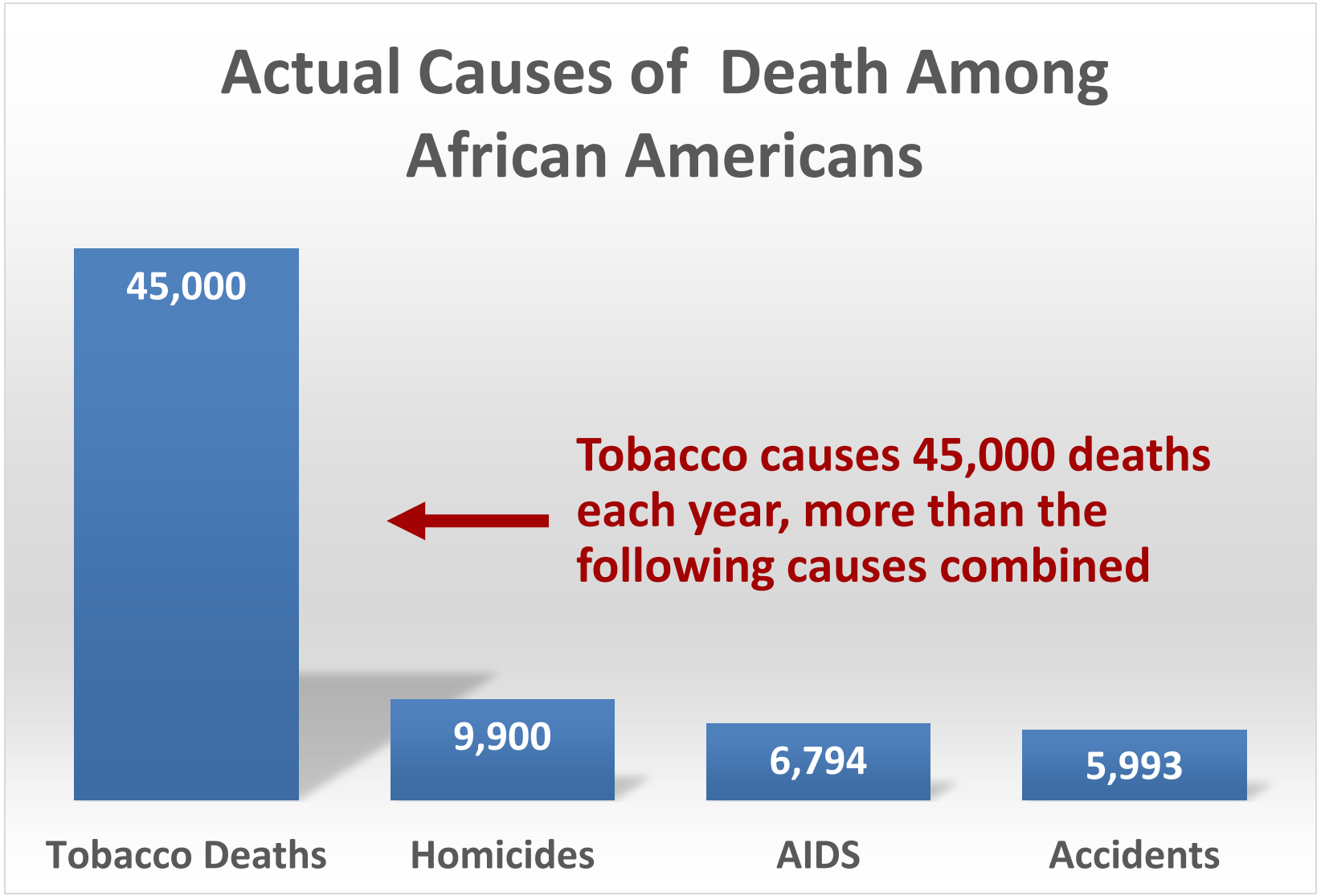
Among Hispanic/Latino current adult smokers and young adult current smokers in the US, **46-47% smoke mentholated cigarettes**

Between 2008-2010 and 2012-2014, the **largest increase in menthol cigarette use** among race/ethnic groups was found in Hispanic smokers (**rising 9.8 percentage points**)


LATINO COORDINATING CENTER
For a Tobacco-Free California

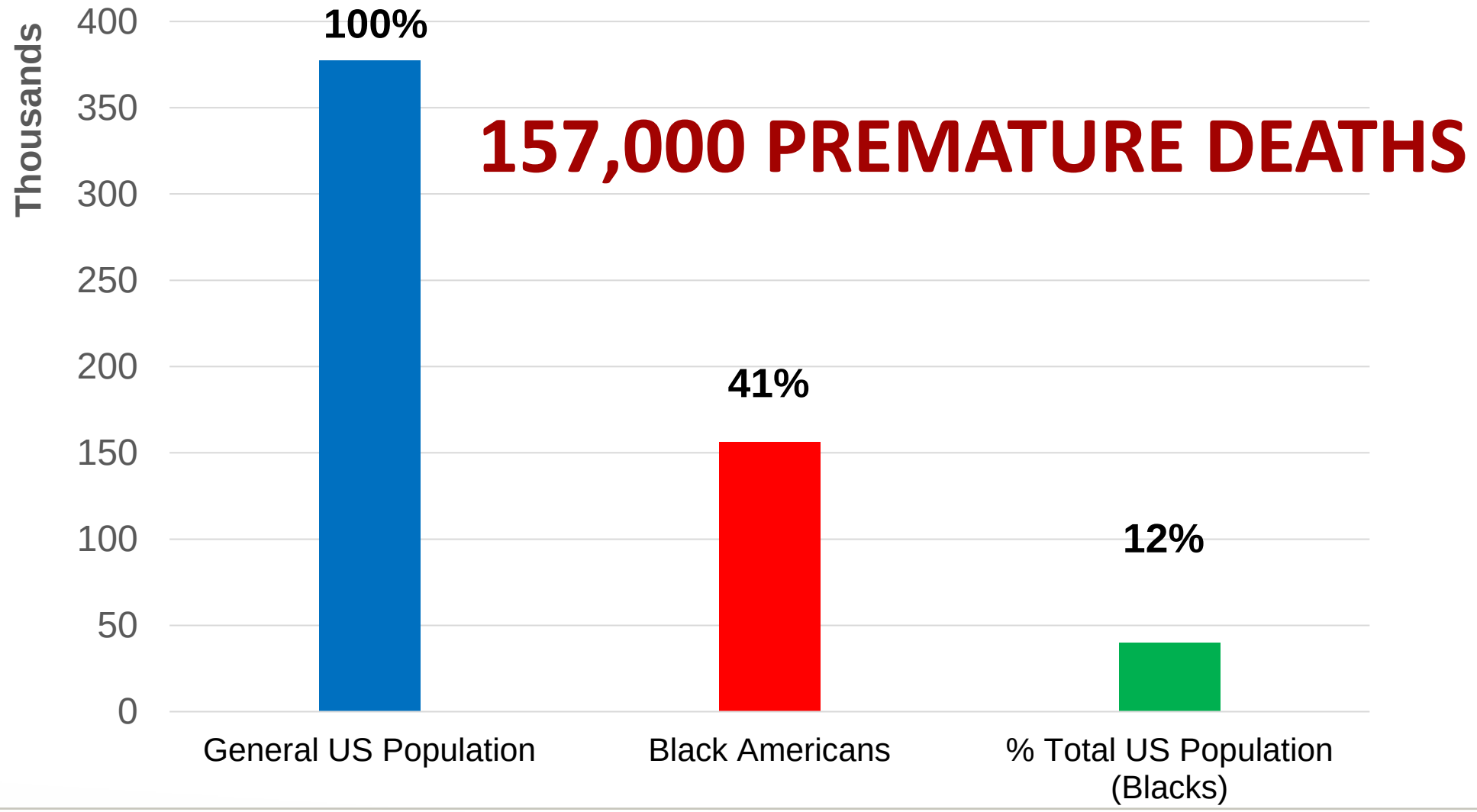
**Menthol is DISPROPORTIONATELY KILLING BLACK PEOPLE!!!**

# Actual Causes of Death Among African Americans



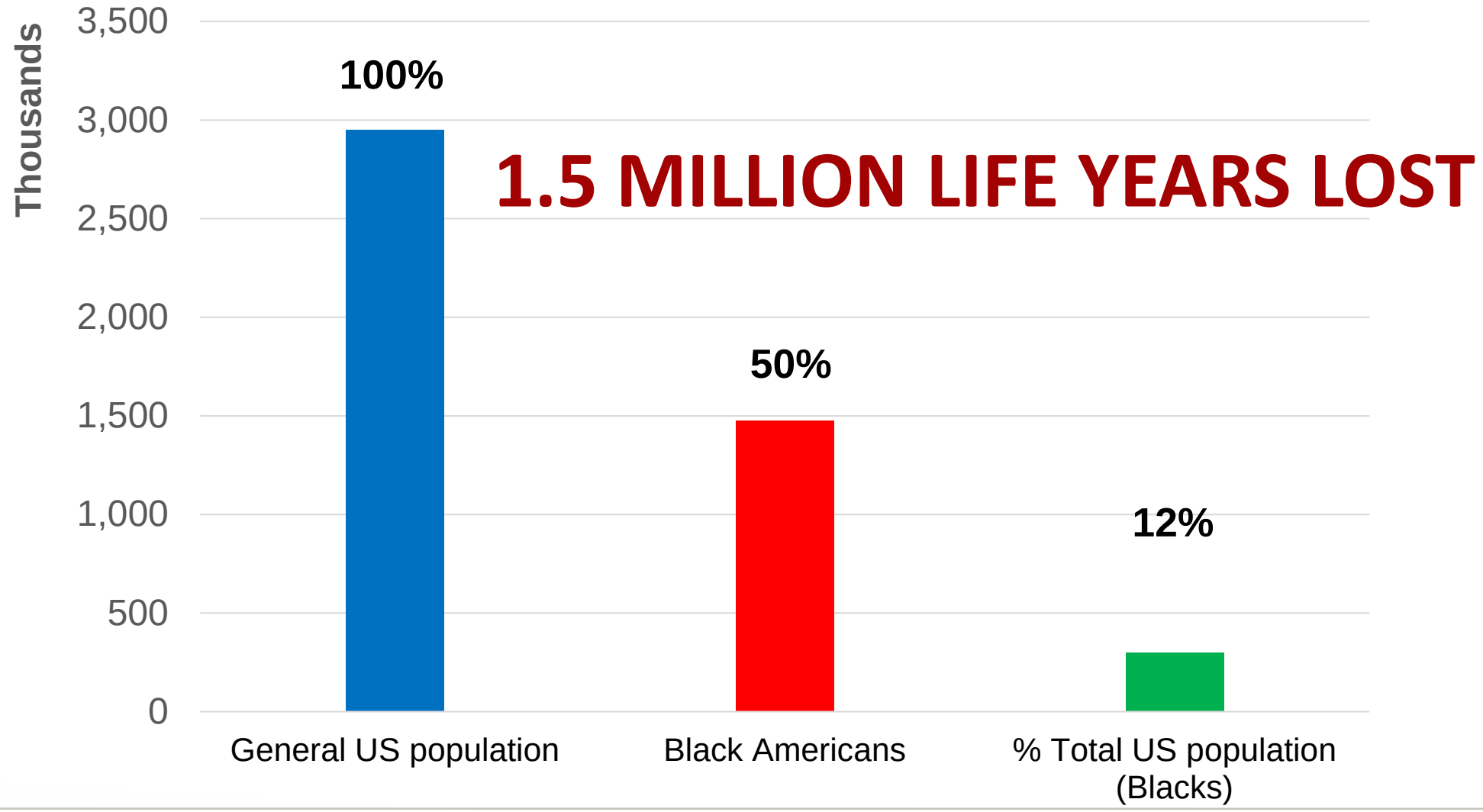

Source: National Center for Injury Prevention and Control, CDC, NCHHSTP AtlasPlus (2019).

# Premature Deaths due to Tobacco (1980-2018)




Mendez D and Le TTT (2021). *Tob Control* -2021-056748

# Life Years Lost due to tobacco (1980-2018)




Mendez D and Le TTT (2021). *Tob Control* -2021-056748

**Between 2009-2020,**
**500,000 African American children**
**started smoking due to menthol cigarettes**

(FDA Tobacco Products Scientific Advisory Committee projection)

# Melanin and Stress

# Tobacco disproportionately affects many subpopulations

- Communities of Color
- Sexual & Gender Minorities
- Military and veterans
- Rural communities
- Unhoused individuals struggling with mental illness
- Youth and adolescents

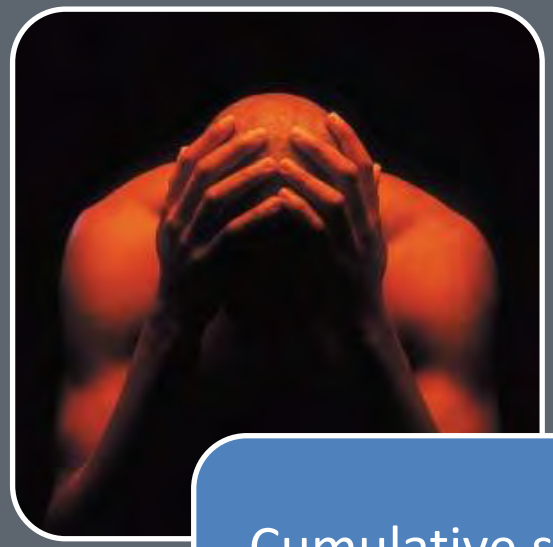
# Demand for “Relief” Must be Addressed

Racism

Discrimination

Poverty

Lack of Educational and Economic Opportunities



Cumulative stress

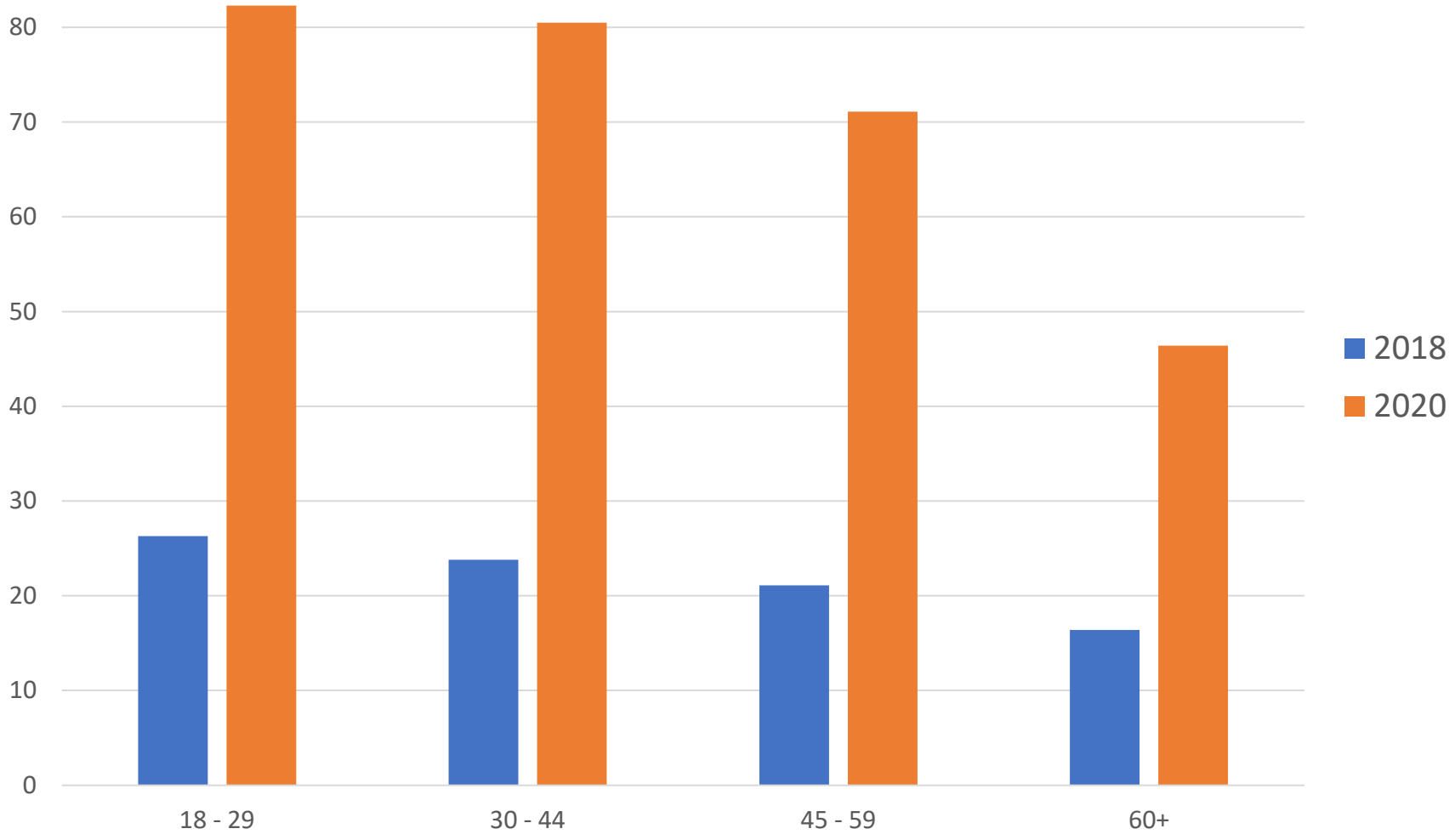
Isolation

Despair

Weathering Effect

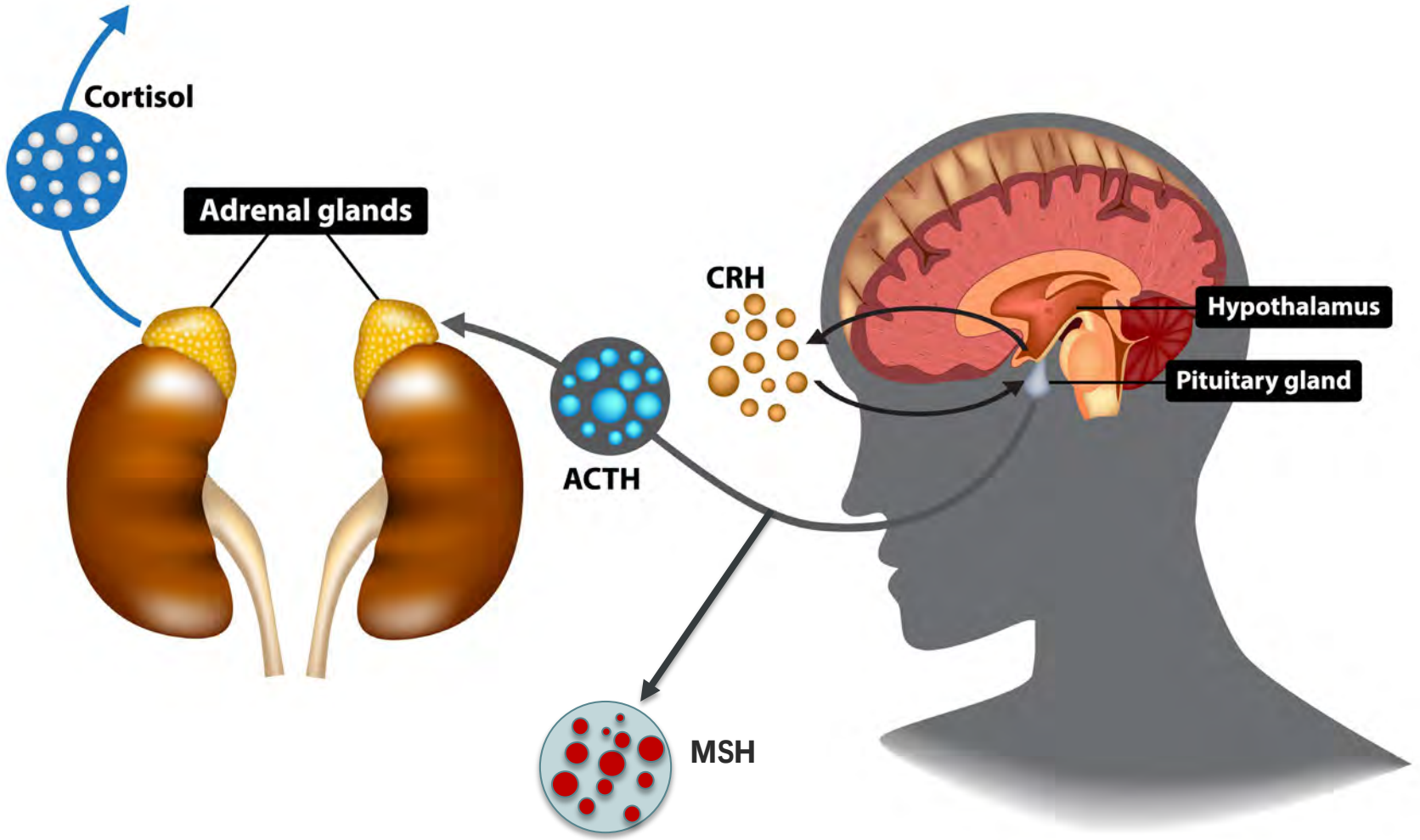
“Coping Mechanisms”

# Mental distress during COVID-19 Pandemic




Twenge, J., & Joiner, T. E. (2020, May 7). Mental distress among U.S. adults during the COVID-19 pandemic. https://doi.org/10.31234/osf.io/wc8ud

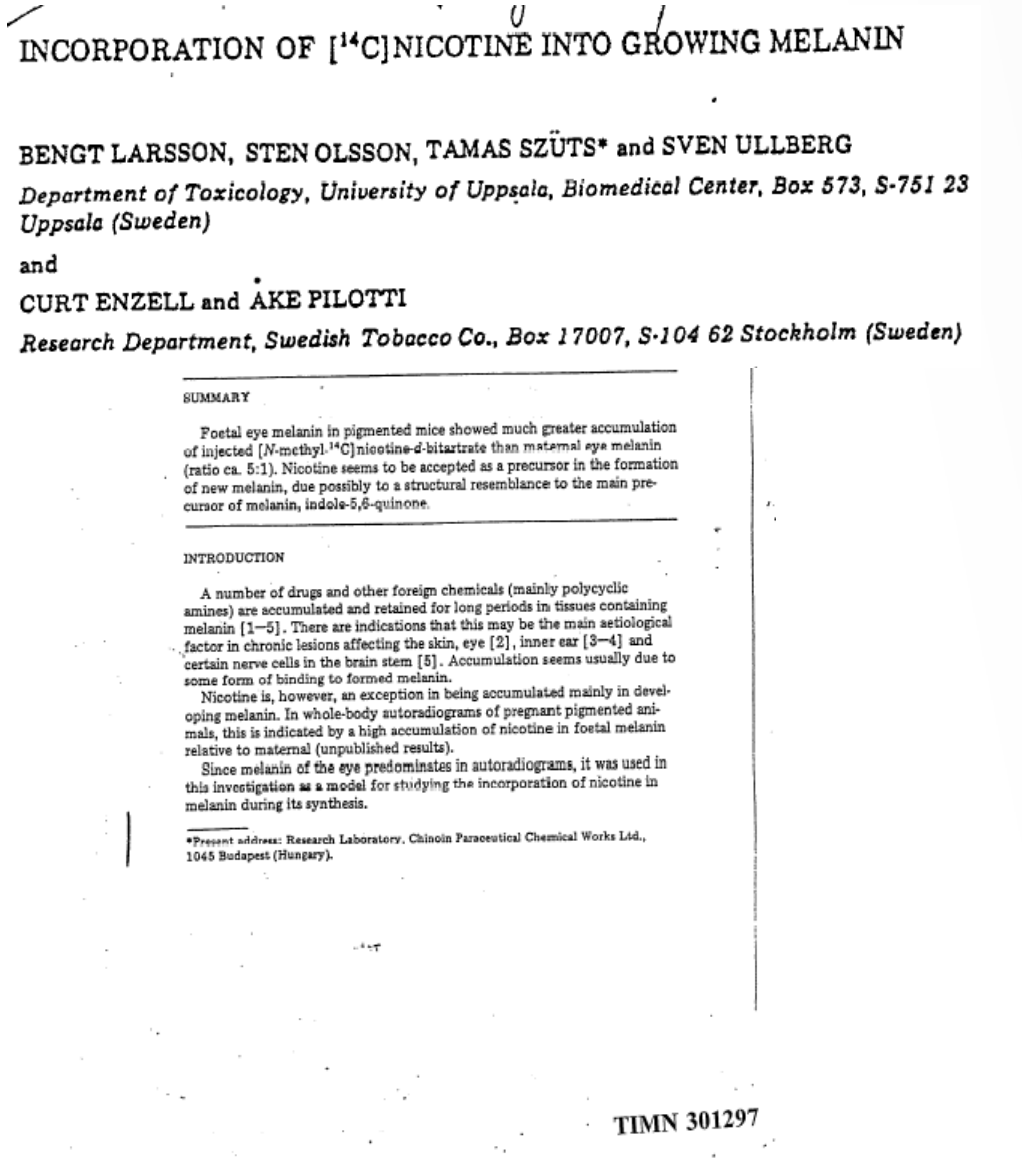
# In stress overload, there is chronic activation of the HPA Axis and cortisol secretion




HYPOTHALAMIC
PITUITARY
ADRENAL
AXIS

# MELANIN LINKED TO NICOTINE DEPENDENCE?

*Due a structural resemblance to the main precursor of melanin, nicotine is accepted as a precursor in the formation of melanin.*



INCORPORATION OF [$^{14}$C]NICOTINE INTO GROWING MELANIN

BENGT LARSSON, STEN OLSSON, TAMAS SZÜTS* and SVEN ULLBERG

*Department of Toxicology, University of Uppsala, Biomedical Center, Box 573, S-751 23 Uppsala (Sweden)*

and

CURT ENZELL and ÅKE PILOTTI

*Research Department, Swedish Tobacco Co., Box 17007, S-104 62 Stockholm (Sweden)*

SUMMARY

Foetal eye melanin in pigmented mice showed much greater accumulation of injected [*N*-methyl-$^{14}$C]nicotine-*d*-bitartrate than maternal eye melanin (ratio ca. 5:1). Nicotine seems to be accepted as a precursor in the formation of new melanin, due possibly to a structural resemblance to the main precursor of melanin, indole-5,6-quinone.

INTRODUCTION

A number of drugs and other foreign chemicals (mainly polycyclic amines) are accumulated and retained for long periods in tissues containing melanin [1—5]. There are indications that this may be the main aetiological factor in chronic lesions affecting the skin, eye [2], inner ear [3—4] and certain nerve cells in the brain stem [5]. Accumulation seems usually due to some form of binding to formed melanin.

Nicotine is, however, an exception in being accumulated mainly in developing melanin. In whole-body autoradiograms of pregnant pigmented animals, this is indicated by a high accumulation of nicotine in foetal melanin relative to maternal (unpublished results).

Since melanin of the eye predominates in autoradiograms, it was used in this investigation as a model for studying the incorporation of nicotine in melanin during its synthesis.

*Present address: Research Laboratory, Chinoin Paraceutical Chemical Works Ltd., 1045 Budapest (Hungary).

TIMN 301297

SEPTEMBER 13, 2023

# FACT SHEET: As Part of President Biden's Unity Agenda, White House Cancer Moonshot Announces New Actions and Commitments to End Cancer as We Know It

AATCLC
Saving Black Lives

# The African American Tobacco Control Leadership Council

Based in San Francisco, California, the AATCLC was formed in 2008 to educate the African Americans and the public about tobacco use and cessation. Composed of a cadre pf dedicated community activists, academics, public health advocates, and researchers, the AATCLC has led the fight to expose the predatory marketing of menthol cigarettes and flavored little cigars in Black communities.

- **The African American Tobacco Control Leadership Council (AATCLC) is launching a coordinated effort to make Emotional Brain Training (EBT) services available for stress management and smoking cessation.** In collaboration with the University of California, San Francisco Smoking Cessation Leadership Center, AATCLC will launch a coordinated effort within three months to promote the use of a free app for anyone new to EBT to gain easily scalable, rapid-acting tools to assist with smoking cessation. EBT has shown long-term effectiveness in treating stress overload, as well as mood and addictive behaviors including smoking.

AATCLC
Saving Black Lives

The African American Tobacco Control Leadership Council

EBT

UCSF Smoking Cessation Leadership Center

UCSF Center for Tobacco Control Research and Education

# BREAKING FREE

# Supply people with something else to reach: “Spiral Up Lite” Mobile App

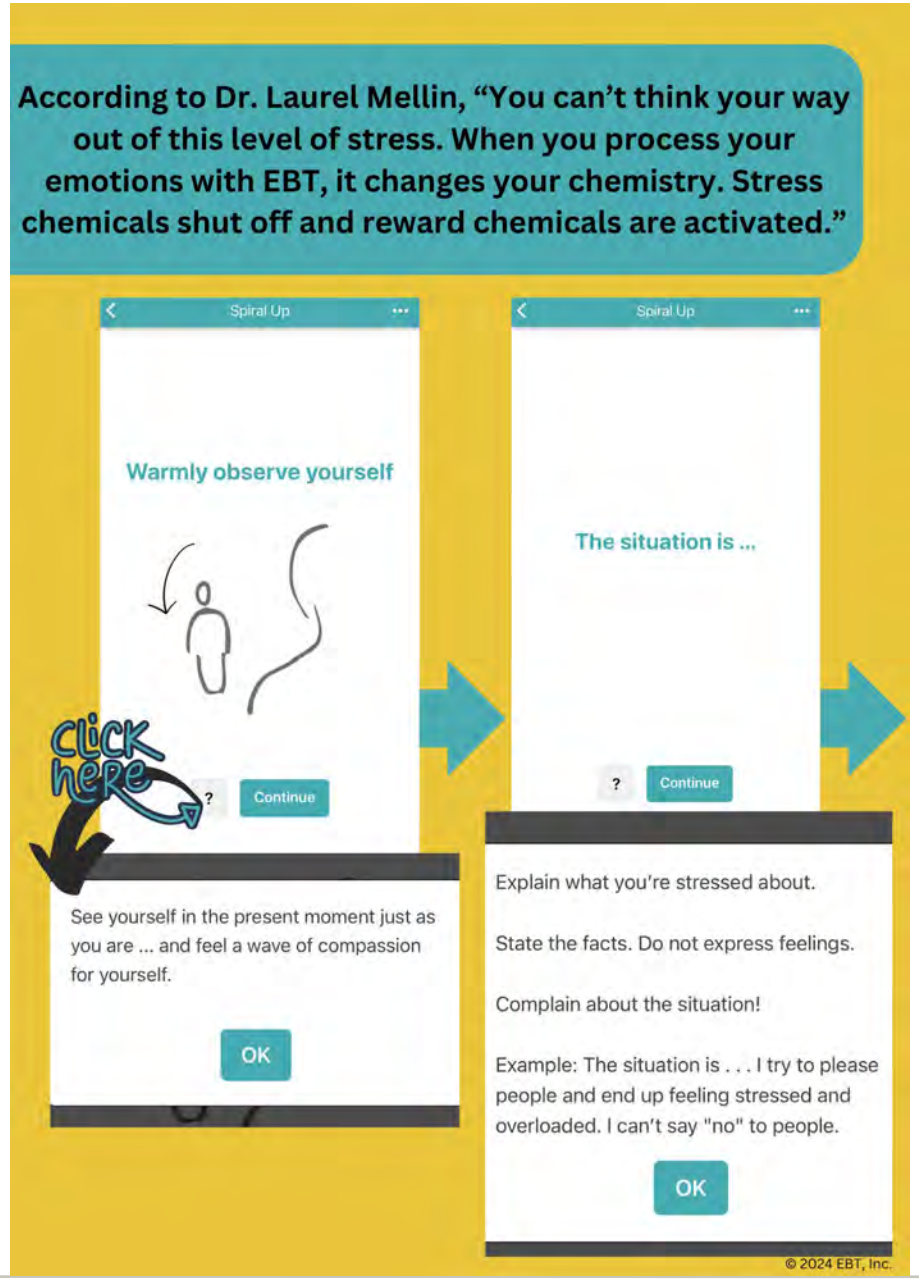
**FREE**

# BREAKING FREE

From Nicotine Special Supplement

## Spiral Up Lite App

***APPLYING EMOTIONAL BRAIN TRAINING (EBT) TO SMOKING CESSATION***


According to Dr. Laurel Mellin, “You can’t think your way out of this level of stress. When you process your emotions with EBT, it changes your chemistry. Stress chemicals shut off and reward chemicals are activated.”
Spiral Up
Warmly observe yourself
Click here
?
Continue
See yourself in the present moment just as you are ... and feel a wave of compassion for yourself.
OK
Spiral Up
The situation is ...
?
Continue
Explain what you’re stressed about.
State the facts. Do not express feelings.
Complain about the situation!
Example: The situation is . . . I try to please people and end up feeling stressed and overloaded. I can’t say "no" to people.
OK
© 2024 EBT, Inc.

# Closing Remarks

Comprehensive menthol/flavor bans will save Black lives and reduce healthcare costs *right now*

As policies are implemented, tailored cessation resources must be provided

Respond to the DEMAND side of tobacco epidemic by addressing root causes

As stress rises, cognitive functioning is affected; access the free mobile app “Spiral Up Lite”