International Agency for Research on Cancer

World Health Organization

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IARC Monographs Meeting 128: Acrolein, Crotonaldehyde, and Arecoline

Questions and Answers (Q&A)

The meeting for *IARC Monographs* Volume 128: Acrolein, Crotonaldehyde, and Arecoline, convened by the International Agency for Research on Cancer (IARC) in Lyon, France, and held remotely, took place on 29 October to 13 November 2020.

The Working Group of international experts, including 20 scientists from 10 countries, evaluated the carcinogenicity of acrolein, crotonaldehyde, and arecoline. After thoroughly reviewing the available scientific literature, the Working Group classified acrolein as *probably carcinogenic to humans (Group 2A)* on the basis of *sufficient evidence* of carcinogenicity in experimental animals and *strong* mechanistic evidence. Crotonaldehyde and arecoline were classified as *possibly carcinogenic to humans (Group 2B)* on the basis of *strong* mechanistic evidence.

The outcome of the assessment has been published in a summary article in *The Lancet Oncology*[1] and will be described in detail in Volume 128 of the *IARC Monographs*, to be published in 2021.

What is acrolein?

Acrolein is a reactive aldehyde. It is a chemical with a high production volume that is used as a reactive intermediate and in the manufacture of numerous chemical products, and as a herbicide in recirculating water systems. Tobacco smoke is a major source of exposure in the general population. Acrolein is also formed during combustion of fuels, wood, and plastics, and is present in ambient air pollution and vapour from electronic cigarettes.

On what basis was acrolein classified in Group 2A?

Acrolein was classified as *probably carcinogenic to humans (Group 2A)* on the basis of *sufficient evidence* of carcinogenicity in experimental animals and *strong* mechanistic evidence.

- *Sufficient evidence* for the carcinogenicity of acrolein in experimental animals was demonstrated in two rodent species: acrolein increased the incidence of malignant neoplasms in mice and increased the incidence of the combination of benign and malignant neoplasms in rats.
- There was *strong* evidence that acrolein exhibits multiple key characteristics of carcinogens: acrolein is electrophilic; it is genotoxic; it alters DNA repair or causes genomic instability; it induces oxidative stress and chronic inflammation; it is immunosuppressive; and it alters cell proliferation, cell death, or

[1] *IARC Monographs* Volume 128 Working Group (2020). Carcinogenicity of acrolein, crotonaldehyde, and arecoline. *Lancet Oncol*, Published online 26 November 2020; https://doi.org/10.1016/S1470-2045(20)30727-0

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nutrient supply. The *strong* evidence was primarily from studies in human primary cells and studies in experimental systems, supported by studies on DNA adducts in humans.

- There was *inadequate evidence* in humans regarding the carcinogenicity of acrolein.

Who is exposed to acrolein?

Acrolein is present in smoke from cigarettes and vapour from electronic cigarettes. It is formed during combustion of fuels, wood, and plastics, and is present in ambient air pollution. In kitchens, there are measurable amounts of acrolein in the air during high-temperature roasting and deep-fat frying. Acrolein also forms endogenously (i.e. within the body). Firefighters are exposed occupationally.

How can people exposed to acrolein reduce their exposure?

Tobacco smoking cessation is an important way for people to reduce their exposure to acrolein. Exposure to acrolein could also be reduced by avoidance of electronic cigarette use, because acrolein is present in the vapour from electronic cigarettes.

What is crotonaldehyde?

Crotonaldehyde is a reactive aldehyde. It is a chemical with a high production volume that is widely used for synthesizing chemical agents used in various industries, including pharmaceuticals, rubber, chemicals, leather, and food and agriculture. Crotonaldehyde is also found in tobacco smoke and in cooking oils heated to a high temperature.

On what basis was crotonaldehyde classified in Group 2B?

Crotonaldehyde was classified as *possibly carcinogenic to humans (Group 2B)* on the basis of *strong* mechanistic evidence.

- There was *strong* evidence that crotonaldehyde exhibits multiple key characteristics of carcinogens: crotonaldehyde is electrophilic; it is genotoxic; it induces oxidative stress; and it induces chronic inflammation. This *strong* evidence was from studies in human primary cells and in various experimental systems.
- There was *limited evidence* of carcinogenicity in experimental animals.
- There was *inadequate evidence* in humans regarding the carcinogenicity of crotonaldehyde.

Who is exposed to crotonaldehyde?

Tobacco smoke is a major source of exposure to crotonaldehyde in the general population. Crotonaldehyde is also formed during combustion of vehicle fuels and wood, and during thermal treatment of foodstuffs. It is found in cooking fires, ambient air pollution, and vapour from electronic cigarettes, as well as in some foods, including cooking oils heated to a high temperature. Crotonaldehyde is also formed endogenously (i.e. within the body). Occupational exposures to crotonaldehyde occur among firefighters and workers in coke ovens, aldehyde manufacture, garages, and toll booths.

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Acrolein and crotonaldehyde were previously evaluated by the Working Group in 1995. Why did the *IARC Monographs* Programme re-evaluate these compounds?

These compounds were both previously evaluated by the Working Group in 1995 as *not classifiable as to its carcinogenicity to humans (Group 3)*. An IARC Advisory Group of independent experts[2] recommended that these compounds be re-evaluated with high priority. A recent high-quality animal bioassay was available for acrolein, and new mechanistic evidence was available for both acrolein and crotonaldehyde.

What is arecoline?

Arecoline is the primary active ingredient of the areca nut. Areca nut has been classified as *carcinogenic to humans (Group 1)*.

On what basis was arecoline classified in Group 2B?

Arecoline was classified as *possibly carcinogenic to humans (Group 2B)* on the basis of *strong* mechanistic evidence.

- There was *strong* evidence that arecoline exhibits multiple key characteristics of carcinogens: arecoline is electrophilic; it is genotoxic; it alters DNA repair or causes genomic instability; and it induces oxidative stress. The *strong* evidence was from studies in human primary cells and in various experimental systems.
- There was *limited evidence* of carcinogenicity in experimental animals.
- There was *inadequate evidence* in humans regarding the carcinogenicity of arecoline.

Who is exposed to arecoline?

Areca nut is widely cultivated in Asia. It has been estimated that more than 10% of the world's population, primarily in south-eastern Asia, chews areca nut for its mild psychoactive effects. Arecoline has been used medicinally as an anthelmintic, and it is still applied in the form of areca nut preparation and as an ingredient in traditional Chinese and Ayurveda medicines. Arecoline is readily absorbed and can be detected in saliva, blood, urine, hair, and breast milk after exposure.

Why did the *IARC Monographs* Programme decide to evaluate arecoline?

An IARC Advisory Group of independent experts[2] recommended that arecoline be evaluated with high priority, on the basis of the available mechanistic evidence.

Why did the *IARC Monographs* Programme evaluate arecoline if areca nut had already been classified as *carcinogenic to humans (Group 1)*?

[2] Marques MM, Berrington de Gonzalez A, Beland FA, Browne P, Demers PA, Lachenmeier DW, et al.; IARC Monographs Priorities Group. Advisory Group recommendations on priorities for the IARC Monographs. *Lancet Oncol*, Published online 18 April 2019; https://doi.org/10.1016/S1470-2045(19)30246-3

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Areca nut is a complex mixture, and the carcinogenic components of this mixture have not been identified. Arecoline is the primary active ingredient of the areca nut, and can be detected in saliva, blood, urine, hair, and breast milk of areca-nut users. Arecoline has also been applied directly in traditional medicines. In terms of properties, arecoline is an alkaloid that has been compared to nicotine. Like nicotine, arecoline acts on the nicotinic acetylcholine receptor; however, arecoline is also a partial agonist of other receptors, including the muscarinic acetylcholine receptors.

Why is this evaluation of arecoline important?

This evaluation is important because it adds to the understanding of how areca nut causes cancer. It has been estimated that more than 10% of the global population, primarily in south-eastern Asia, chews areca nut for its mild psychoactive effects. This evaluation indicates that arecoline is *possibly carcinogenic to humans (Group 2B)*.

Where do the studies on arecoline come from?

The studies evaluated came primarily from mechanistic investigations in laboratories around the world, including in south-eastern Asia, where areca-nut use is prevalent.

Where can one find more information about the *IARC Monographs* Programme?

For more information about the *IARC Monographs* Programme and classifications, see:

https://monographs.iarc.fr/wp-content/uploads/2018/07/QA_ENG.pdf

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