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Toxicologic profile of acrylonitrile

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Acrylonitrile is a monomer used extensively as a raw material in the manufacturing of acrylic fibers, plastics, synthetic rubbers, and acrylamide. It has been classified as a probable human carcinogen according to the results of numerous chronic rat bioassays. The present report summarizes the toxicity data on acrylonitrile and reviews available data concerning the mechanism (genetic versus epigenetic) by which acrylonitrile is carcinogenic in rats. From the evaluation of the relevant toxicity data, it can be concluded that acrylonitrile is indeed carcinogenic to rats after either oral or inhalational exposure. However, information on other mammalian species is lacking, and, moreover, the exact mechanism of the carcinogenic process is unclear. Therefore, it is recommended to conduct an additional long-term inhalation carcinogenicity study with acrylonitrile in mice, as well as studies into the mechanism by which acrylonitrile induces (brain) tumors in rats (genetic versus epigenetic).

Key terms carcinogenicity, inhalation, mechanism, oral, toxicity.

Acrylonitrile is a monomer used extensively as a raw material in the manufacture of acrylic fibers, plastics, synthetic rubbers, and acrylamide. Apart from occupational exposure, concerns have been raised pertaining to potential exposure of the general public to acrylonitrile from food packaging and other consumer products. Numerous chronic rat bioassays have been conducted by various routes to provide a better understanding of the potential of acrylonitrile to cause cancer in humans. In the United States, the Environmental Protection Agency (1, 2) classified acrylonitrile as a group B1 chemical (probable human carcinogen) based on an increase in lung cancer among exposed workers and on an increase in the incidence of brain tumors in rats exposed to acrylonitrile by the inhalational and oral route.

The International Agency for Research on Cancer (3) classified acrylonitrile as a group 2A carcinogen (probable human carcinogen) based on sufficient evidence from laboratory animals and limited evidence from humans. The Health Council of The Netherlands (4) determined that acrylonitrile was carcinogenic in laboratory animals, but the evidence for humans was very weak.

The purpose of this paper is to present the overall toxicologic profile of acrylonitrile with the aim of elucidating the mechanism by which acrylonitrile is carcinogenic in rats.

Toxicokinetics

The data presented in this section have been taken from references 5—7 and from an unpublished report (Bos PMJ. The health-based recommended occupational exposure limit for acrylonitrile: draft report from the Dutch expert committee on occupational standards of the directorate-general of labor. The Hague, 1993:62 p).

Following inhalational or oral exposure, acrylonitrile absorption was shown to be rapid and extensive (90—98%), and distribution appeared rapidly throughout the body, with little significant accumulation in a particular organ. Seventy-two hours after the oral administration of radiolabeled acrylonitrile to F344 rats and B6C3F1 mice, the recovery of radioactivity ranged from 79% to 94% in urine and from 2% to 8% in feces.

The biotransformation of acrylonitrile occurs via 2 pathways: (i) conjugation with glutathione (GSH) and (ii) oxidation by cytochrome P450, resulting in the formation of the epoxide 2-cyanoethylene oxide (CEO). CEO is mutagenic and reacts much faster with DNA (deoxyribonucleic acid) than acrylonitrile. Therefore CEO is thought to play an important role in the carcinogenic properties of acrylonitrile.

In vitro experiments with liver microsomes have shown that the hepatic oxidation of acrylonitrile to CEO is high-

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