# Carcinogenicity of tris(chloropropyl) phosphate, butyraldehyde, and cumyl hydroperoxide

In March, 2026, a Working Group of 12 scientists from nine countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to finalise their evaluation of the carcinogenicity of tris(chloropropyl) phosphate (TCPP), butyraldehyde, and cumyl hydroperoxide.

TCPP was classified as "probably carcinogenic to humans" (Group 2A) based on the combination of "sufficient" evidence for cancer in experimental animals and "strong" mechanistic evidence in human primary cells. Butyraldehyde was classified as "possibly carcinogenic to humans" (Group 2B) based on "sufficient" evidence for cancer in experimental animals and on "strong" mechanistic evidence in experimental systems. Cumyl hydroperoxide was classified as "possibly carcinogenic to humans" (Group 2B) based on "strong" mechanistic evidence in human primary cells and experimental systems. These assessments will be published in Volume 141 of the *IARC Monographs*.[1]

TCPP, a mixture of four isomers, is a high-production-volume (HPV) chemical widely used as an additive flame retardant in polyurethane foams, plastics, textiles, and construction materials. It has been detected in most environmental matrices, but levels are generally higher indoors, where dust acts as a reservoir. Occupational exposure occurs during the manufacture, use, and disposal of materials and products containing TCPP, but also in other occupational settings, such as offices, through furnishings and electronic and electrical equipment. In the general population, exposure to TCPP is widespread, occurring via indoor air and dust, consumer products, and the diet, and is highest among young children with frequent hand-to-mouth behaviour. TCPP is absorbed via ingestion, inhalation, and dermal contact. It is metabolised in the liver and is excreted largely in urine. The compound and its metabolites have also been detected in human plasma and breast milk.

In B6C3F$_1$ mice, oral administration of TCPP increased the incidence of hepatocellular carcinoma in males, and hepatocholangiocarcinoma was observed in one mouse in each of two treated groups. In females, TCPP increased the incidence of hepatocellular carcinoma and hepatocellular adenoma or carcinoma (combined).[2] In Sprague-Dawley rats, oral administration of TCPP increased the incidence of hepatocellular carcinoma and hepatocellular adenoma or carcinoma (combined) in males. In females, TCPP increased the incidence of adenocarcinoma of the uterus and adenoma or adenocarcinoma (combined) of the uterus; squamous cell carcinoma of the uterus was observed in one mouse in each of two treated groups.[2]

TCPP exhibits consistent and coherent evidence of the key characteristics of carcinogens (KCs) in human primary cells and experimental systems. TCPP is genotoxic in human peripheral blood mononuclear cells and umbilical vein endothelial cells, and in mice. It increased DNA strand breaks and the frequency of micronuclei. Multiple studies in human primary cells and in experimental systems showed that TCPP increased levels of reactive oxygen species. TCPP induces chronic inflammation in experimental systems. It increased proinflammatory cytokines in human cell lines and mouse adipocytes and induced chronic inflammation in the liver of rats after 3 months or 2 years of exposure.[2] TCPP modulates receptor-mediated effects. It acted in the thyroid-hormone signalling pathway, including as a thyroid receptor β antagonist, in experimental systems in vitro. High-throughput data in human cells showed that TCPP acts as a PXR/CAR agonist. In addition, TCPP alters cell proliferation, cell death, or nutrient supply in experimental systems in vivo in rodents and zebrafish.

The evidence regarding cancer in humans was "inadequate". Six case–control studies measured TCPP or its metabolites in blood, urine, dust samples, or wristbands, mostly in relation to thyroid cancer. However, the findings were inconsistent, and there were concerns about study design and exposure misclassification.

Butyraldehyde is an HPV chemical, and most of its production is used on-site as a chemical intermediate, mainly for the production of *n*-butanol, butyric acid, 2-ethylhexanol, polyvinyl butyral, and plasticisers. Butyraldehyde occurs naturally in some plants and foods and is formed during combustion of biomass. Occupational exposure occurs mainly via inhalation during chemical manufacturing, food service, health care, firefighting, and charcoal production settings, although quantitative measurements were sparse. The general population is exposed primarily through inhalation of air and cigarette smoke, and through dietary intake from natural food occurrence, use as a flavouring agent, and cooking-related formation.

Butyraldehyde is produced endogenously through lipid peroxidation of polyunsaturated fatty acids and hepatic oxidation of *n*-butanol. The few available studies did not show external exposure to have an important impact on blood levels, but exposure is expected at the site of absorption. Butyraldehyde

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**Upcoming meetings**
June 9–16, 2026: Butyl benzyl phthalate, dibutyl phthalate, and diisononyl phthalate

Nov 3–10, 2026: Cannabis smoking

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has been detected in human blood, brain, urine, and exhaled breath, indicating systemic distribution to various tissues. Human alcohol dehydrogenases oxidise *n*-butanol to butyraldehyde, and butyraldehyde can be also reduced back to *n*-butanol by aldehyde reductases. The human alcohol dehydrogenase has also shown dismutase activity. Butyraldehyde was found to be synthesised from *n*-butanol in rat liver microsomes, and in bacteria that can colonise the human oral cavity and the gastrointestinal tract.

In F344/DuCrlCrlj rats treated by inhalation (whole body), butyraldehyde caused an increase in the incidence of squamous cell carcinoma of the nasal cavity in males. Adenosquamous carcinoma, carcinosarcoma, and sarcoma of the nasal cavity and squamous cell carcinoma of the larynx were each observed in one animal. In females, butyraldehyde caused an increase in the incidence of squamous cell carcinoma of the nasal cavity and squamous cell carcinoma or squamous cell papilloma (combined) of the nasal cavity.[3]

Butyraldehyde exhibits consistent and coherent evidence for the KCs in experimental systems. Butyraldehyde induces chronic inflammation; it altered miRNAs related to cytokine signalling and increased IL-6 and IL-8 secretion in a human alveolar epithelial cell line. In rats, 2-week inhalation exposure induced inflammation of the nasal cavity; 2-year exposure induced rhinitis at tumour sites and foreign-body inflammation in the lungs.[3] Butyraldehyde alters cell proliferation, cell death, and nutrient supply. Hyperplasia was observed in the nasal cavity of rats after 2 weeks and 13 weeks of inhalation exposure, and squamous cell metaplasia and hyperplasia of the respiratory epithelium and larynx, basal cell hyperplasia, and atrophy of the olfactory epithelium were also observed after 2 years.[3] In addition, butyraldehyde inhibited gap junctions in human primary cells.

Cumyl hydroperoxide is an HPV chemical produced by oxidation of cumene. It is used as a polymerisation catalyst, for the cross-linking of sulphide rubbers, and as an intermediate in the production of acetone and phenol. Occupational exposure may occur through inhalation of vapours or dermal contact during manufacturing and handling processes, although data were sparse. No data were available for general population exposure. In experimental systems, cumyl hydroperoxide was metabolised by cytochrome P450s, producing cumyl peroxyl and cumyloxyl radicals.

Cumyl hydroperoxide exhibits consistent and coherent evidence for the KCs in human primary cells and experimental systems. Cumyl hydroperoxide is genotoxic and induces oxidative stress. In human lymphocytes, it induced DNA damage and micronuclei. In mammalian cells in vitro, cumyl hydroperoxide induced DNA damage, micronuclei, and gene mutations; in mice, it induced DNA damage and dominant lethal germ-cell mutations. Cumyl hydroperoxide increased levels of reactive oxygen species, enhanced oxidative damage to lipids, and altered antioxidant levels or enzyme activities. Cumyl hydroperoxide induces chronic inflammation. In 14-day and 90-day studies, rodents showed histopathological changes of the skin, including epidermal alterations, dermal fibrosis, and chronic active inflammation.[4] An increase in levels of multiple inflammatory markers was reported in human skin cells. Cumyl hydroperoxide alters cell proliferation, cell death, or nutrient supply. In mice, cumyl hydroperoxide used as a stage I and II tumour promoter was found to increase DNA synthesis, induce ornithine decarboxylase in epidermis, and activate AP-1 in the skin, where some increase in the incidence of carcinoma was observed.[5] It also induced epidermal, hair follicle, and sebaceous gland hyperplasia in mice and rats.[4] The evidence regarding cancer in experimental animals was "limited".

For both butyraldehyde and cumyl hydroperoxide, the human cancer evidence was "inadequate", as no informative studies were available.

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