

# Report on Carcinogens (RoC), Twelfth Edition

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## The RoC is congressionally mandated

- Public Health Service Act, Section 301(b)(4) (1978)
  - Directs HHS Secretary to annually publish a list of carcinogens
  - Changed to a biennial report (1992)
- Preparation delegated to the National Toxicology Program (NTP)
  - Dr. Ruth Lunn, Director, Office of the Report on Carcinogens
- RoC is cumulative -- each edition adds newly listed substances to prior list
  - 1st RoC published in 1980 had 26 listings
  - 12th RoC published in 2011 has 240 listings
    - 54 known human carcinogens, 186 reasonably anticipated to be human carcinogens



## The RoC identifies potential cancer hazards

- Not a regulatory document -- merely identifies hazards
  - Lists agents, substances, mixtures, or exposure circumstances that may pose a cancer hazard for people in the United States
  - Lists substances as “*known*” or “*reasonably anticipated human carcinogens*”
- Evaluated for listing using established criteria
  - *Known human carcinogen*: sufficient evidence of cancer from human studies showing the substance causes cancer
  - *Reasonably anticipated human carcinogen*:
    - Limited evidence from studies in humans
    - or
    - Sufficient evidence from studies in experimental animals
    - or
    - Member of a class of listed substances or causes biological effects which would likely cause cancer in humans

# Each listed substance has a profile containing

## • Listing status

- Known or reasonably anticipated human carcinogen

## • Summary of studies that support the listing

- Humans
- Laboratory animals
- Mechanisms

## • Information on

- Physical properties
- Use and production
- Sources of exposure
- Current Federal regulations and guidelines to limit exposures

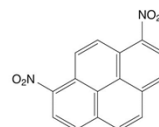
### Substance Profiles

### Nitroarenes: 1,8-Dinitropyrene

#### 1,8-Dinitropyrene

CAS No. 42397-65-9

Reasonably anticipated to be a human carcinogen  
First listed in the *Eighth Report on Carcinogens* (1998)



#### Carcinogenicity

1,8-Dinitropyrene is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals.

#### Cancer Studies in Experimental Animals

1,8-Dinitropyrene caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. Subcutaneous injection of 1,8-dinitropyrene caused cancer at the injection site (sarcoma) in male mice and in rats of both sexes and leukemia in female rats (IARC 1989). Exposure by intraperitoneal injection caused myelocytic leukemia and cancer of the peritoneal cavity (sarcoma) and mammary gland (adenocarcinoma) in female rats. Administration of 1,8-dinitropyrene to female rats by stomach tube also caused mammary-gland cancer (adenocarcinoma).

#### Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 1,8-dinitropyrene.

#### Studies on Mechanisms of Carcinogenesis

Pathways of 1,8-dinitropyrene metabolism leading to mutagenic and clastogenic metabolites and formation of DNA adducts have been described (IARC 1989). Reactive products of 1,8-dinitropyrene are formed by metabolism through two reductions of the 1-nitro group to form first a nitroso and then a *N*-hydroxy amino group at the 1-position (Beland 1986). Activation occurs by *O*-acetylation of the *N*-hydroxylamine group followed by removal of the acetate to create the active nitrenium ion, which reacts with deoxyguanosine at C-8 to form the DNA adduct.

1,8-Dinitropyrene is genotoxic in a wide variety of assays in bacteria and mammalian cells (IARC 1989). In *Salmonella typhimurium*, the most frequent mutations were C:G to A:T or G:C transversions (Watanabe *et al.* 1997), and a metabolite of 1,8-dinitropyrene, 1-nitroso-8-nitropyrene, caused mutations at G:C base pairs and frameshift mutations (Lambert *et al.* 2001). 1,8-Dinitropyrene also caused morphological transformation of cultured hamster embryo cells (IARC 1989). Exposure of SV40-transformed hamster ovary cells to 1,8-dinitropyrene caused formation of DNA adducts and amplified SV40 DNA (Neft 1993).

There is no evidence to suggest that the mechanisms by which 1,8-dinitropyrene causes tumors in experimental animals would not also operate in humans.

#### Properties

1,8-Dinitropyrene is a nitro-substituted polycyclic aromatic hydrocarbon that exists at room temperature as a yellow fluffly or light-brown

crystalline solid (IARC 1989). It has a molecular weight of 292.3 and a melting point of over 300°C (HSDB 2009).

#### Use

1,8-Dinitropyrene has been reported to be a photosensitizer; however, there is no evidence that it has ever been used commercially for this or any other purpose (IARC 1989). 1,8-Dinitropyrene is available for research purposes at a purity of at least 99% and in <sup>14</sup>C- or <sup>3</sup>H-labeled form at a radiochemical purity of at least 98%.

#### Production

In 2009, no commercial producers of 1,8-dinitropyrene were identified worldwide, but 1,8-dinitropyrene was available from two U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of 1,8-dinitropyrene were found.

#### Exposure

The routes of human exposure to 1,8-dinitropyrene are inhalation, ingestion, and dermal contact (IARC 1989). In Japan, 1,8-dinitropyrene was detected in soil samples in various regions of the country (Watanabe *et al.* 1998, 1999, 2000, 2003, 2005). No data were found on occupational exposure to 1,8-dinitropyrene. (See also the discussion of exposure in the Introduction for Nitroarenes [Selected], above.)

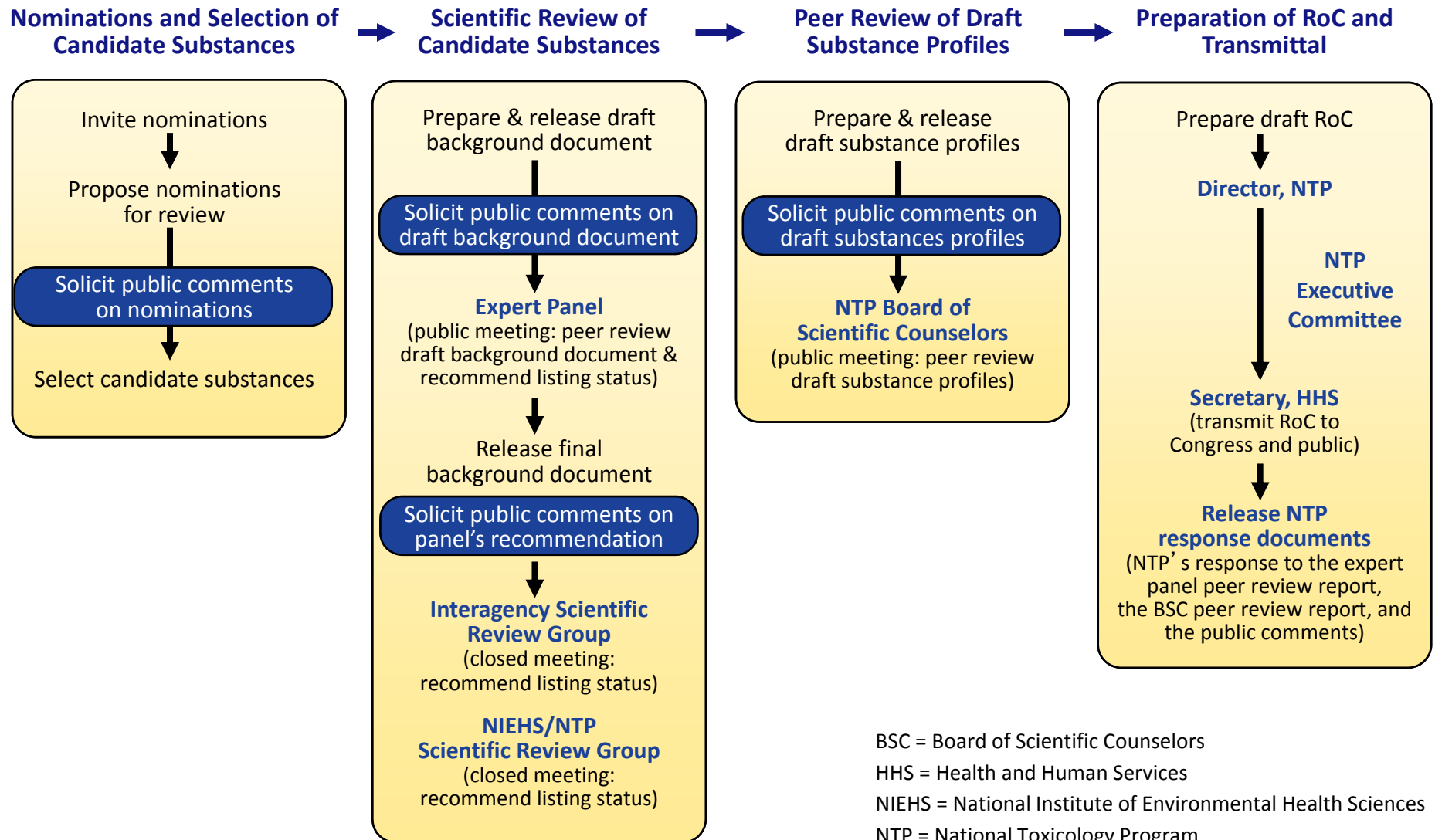
#### Regulations

No specific regulations or guidelines relevant to reduction of exposure to 1,8-dinitropyrene were identified.

#### References

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# Preparation of the 12<sup>th</sup> RoC followed an established process (scientific input, external peer review, public comments)



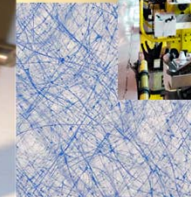
BSC = Board of Scientific Counselors  
 HHS = Health and Human Services  
 NIEHS = National Institute of Environmental Health Sciences  
 NTP = National Toxicology Program  
 RoC = Report on Carcinogens

## Who uses the RoC?

- Regulatory and health research agencies to inform public health decisions
  - OSHA Hazard Communication Standard (MSDS)
  - California Proposition 65 (Safe Drinking Water Act 1986)
  - U.S. EPA -- Criteria for the Evaluation of Permit Applications for Ocean Dumping of Materials under TSCA
- Public
  - Provides information about potential cancer hazards to allow informed decisions about limiting exposures
- Scientific community
  - RoC and background documents available on PubMed and NTP website
- Stakeholders
  - Identifies cancer hazards for labeling and worker protection

## Release of the 12<sup>th</sup> RoC generated public interest

- Approximately 500 news articles published in the first 10 days from release
- Website traffic in the first 7 days after release
  - Over 35,000 RoC-related PDFs downloaded
  - 26.3 thousand visits to the NTP website
  - 64.3 thousand page views of the NTP website
  - Most interest: formaldehyde and styrene



## Newly reviewed listings in the 12<sup>th</sup> RoC

Substance	Type of Agent	Listing Status	Public interest
Aristolochic acids	Botanical	KHC	Low to moderate
Captafol	Fungicide	RAHC	Low
Cobalt-tungsten carbide: powders and hard metals	Metal	RAHC	Moderate
Formaldehyde	Industrial chemical	KHC	High
Certain glass wool fibers (inhalable)	Synthetic fibers	RAHC	High
<i>ortho</i> -Nitrotoluene	Industrial chemical	RAHC	Low
Riddelliine	Botanical	RAHC	Low
Styrene	Industrial chemical	RAHC	High

KHC = Known to be a human carcinogen; RAHC = Reasonably anticipated to be a human carcinogen



## Aristolochic Acids: *Known to be human carcinogens*

- How are people exposed to aristolochic acids (AA)?
  - Intentional or inadvertent use of herbal remedies containing AA
  - Still can be purchased on the Internet despite FDA warning and bans in other countries
- What is the scientific evidence supporting the listing?
  - Increased risks of urothelial cancer (upper urinary tract and urinary bladder) in individuals consuming botanical products containing AA
  - Mechanistic studies showing AA are the carcinogenic components of the botanical products



## **Captafol: *Reasonably anticipated to be a human carcinogen***

- How were people exposed to captafol?
  - Past exposure (occupational, environmental, and in food) from its use as a fungicide
  - Banned in the United States (by FDA) and in other countries
- What is the scientific evidence supporting the listing?
  - Sufficient evidence from studies in experimental animals: multi-site carcinogen
  - Supporting studies show captafol is genotoxic

## ***ortho*-Nitrotoluene: Reasonably anticipated to be a human carcinogen**

- How are people exposed to *o*-nitrotoluene?
  - Primarily in the workplace during the manufacture of azo dyes, other dyes, and certain agricultural chemicals; also used as an intermediate in the synthesis of explosives
  - Potential environmental exposure: breakdown product of TNT found near munitions production or military training facilities
- What is the scientific evidence supporting the listing?
  - Sufficient evidence from studies in laboratory rodents: multi-site carcinogen
  - Supporting mechanistic studies: reactive metabolite found in humans

## Riddelliine: *Reasonably anticipated to be a human carcinogen*

- How are people exposed to riddelliine?
  - Primarily from the environment: riddelliine is found in certain plants (primarily *Senecio*); potential for contamination of food
  - Herbal product or teas: mainly inadvertent use
  - FDA alert: recommended products containing pyrrolizidine alkaloids (such as riddelliine) be removed from the market
- What is the scientific evidence supporting the listing?
  - Sufficient evidence from studies in laboratory animals: multi-site carcinogen
  - Supporting mechanistic studies show that riddelliine is genotoxic



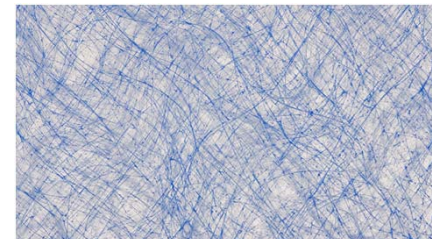
## Cobalt-Tungsten Carbide (CoWC): powders and hard metals: *Reasonably anticipated to be a human carcinogen*

- How are people exposed to CoWC?
  - In the workplace during the manufacturing and grinding of tools
- What is the scientific evidence supporting the listing?
  - Limited evidence from studies in humans: lung cancer
  - Supporting mechanistic studies: Co is solubilized from CoWC; cobalt is carcinogenic in animal studies, and CoWC is genotoxic in the mouse lung



## Certain glass wool fibers (inhalable): *Reasonably anticipated human carcinogens*

- How are people exposed to glass wool fibers?
  - In the workplace during their manufacture
  - Installing or removing glass wool products
- What is the scientific evidence supporting the listing?
  - Glass wools (respirable) were first listed in the 7<sup>th</sup> RoC as *reasonably anticipated human carcinogens* because they cause cancer in laboratory animals
  - Studies published since the first listing show that only certain fibers -- inhalable and biopersistent -- are likely to cause cancer in humans
  - In general, insulation glass wool fibers are less likely to cause cancer than more durable “special purpose fibers” used for filtration



## ***Styrene: Reasonably anticipated to be a human carcinogen***

- How are people exposed to styrene?
  - In the workplace; the reinforced plastics and the styrene-butadiene rubber industries
  - In the environment from smoking, indoor air, and foods
- What is the scientific evidence supporting the listing?
  - Studies of styrene-exposed workers provide evidence of genetic damage in lymphocytes and “limited evidence” of lymphohematopoietic cancers
  - Studies of laboratory mice provide “sufficient evidence” of lung tumors
  - Styrene is metabolized to styrene-7,8-oxide, which is listed as a *reasonably anticipated human carcinogen* in the RoC
    - Styrene-7,8-oxide is found in the blood of styrene-exposed workers

## Formaldehyde: *Known to be a human carcinogen*

- How are people exposed to formaldehyde?
  - In the workplace, including industrial workers (manufacturers and users), and in occupations such as embalmers and health professionals
  - In the home from off-gassing of construction products and home-furnishings, and from consumer goods such as hair straighteners
- What is the scientific evidence supporting the listing?
  - Studies of formaldehyde-exposed workers show elevated rates of myeloid leukemia and nasopharyngeal and sinonasal cancers
  - Formaldehyde causes genetic damage (DNA adducts, DNA-protein cross links)





## Several NCI studies were used in the evaluation of formaldehyde

- NCI nested case-control studies of embalmers -- Hauptmann *et al.* 2009
  - “Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde” (*JNCI*)
- NCI cohort of industrial workers exposed to formaldehyde
  - Series of publications, most recent by Hauptmann *et al.* 2003, 2004 and Beane Freeman *et al.* 2009 (*JNCI*) (*Am J Epi*)
- Molecular epidemiology study of Chinese workers -- Zhang *et al.* 2009
  - “Occupational exposure to formaldehyde, hematotoxicity, and leukemia-specific chromosome changes in cultured myeloid progenitor cells” (*Can Epi Bio Prev*)

## Formaldehyde exposure and myeloid leukemia

- Consistent findings across informative studies
  - Excess risks among individuals with high exposure in large cohort studies of industrial and garment workers (NCI and NIOSH studies)
  - Excess risk in the NCI nested case-control study of embalmers
  - No negative findings in reports of studies that specifically evaluated myeloid leukemia with adequate power to detect an effect
  - Recent meta-analysis: Positive association among workers with the highest exposure: RR = 2.47, 95% CI = 1.31 to 2.67 (Schwik *et al.*, *J. Occup Environ Med* 52(9): 878-886, 2010)
- Positive exposure-response relationships found in two studies: embalmers study and NCI cohort study of industrial workers
- Unlikely to be explained by confounding
  - Excess risk found in different industries and occupations (e.g., garment workers, formaldehyde production workers, and embalmers)

## Formaldehyde exposure and nasopharyngeal and sinonasal cancers

- Nasopharyngeal cancer (NPC)
  - Consistent findings of increased NPC among individuals with the highest exposures in several case-control studies and the NCI cohort study of industrial workers
  - Positive exposure-response relationships in the NCI cohort study and a large case-control study (Vaughan et al., *Occup Environ Med* 57(6) 376-384, 2000)
  - Elevated risks remained after consideration of potential confounding by tobacco smoking, wood dust, or other occupational carcinogens
- Sinonasal cancer (SNC)
  - Consistent findings of increased SNC among exposed individuals in several case-control studies and a pooled analyses of 12 case-control studies (Luce et al., *Cancer Causes Control* 13(2) 147-157, 2002)
  - Higher risks among individuals with higher exposures
  - Increased risks found among subjects with little or no exposure to wood dust or after adjusting for wood dust

## Thank You, Questions?

<http://ntp.niehs.nih.gov/roc12/INDEX7317.HTM>

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