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PRINTING PROCESSES AND PRINTING INKS

PRINTING PROCESSES (OCCUPATIONAL EXPOSURES) (Group 2B)

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5. Summary of Data Reported and Evaluation

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5.1 Exposure data

Printing inks are mixtures of three main types of ingredients: pigments, vehicles and additives. Pigments used in printing inks include both inorganic pigments such as carbon black and titanium dioxide and organic pigments, which are frequently dyes rendered insoluble by complexing with a metal ion. Most organic pigments are prepared from azo, anthraquinone and triarylmethane dyes, and phthalocyanines.

There are five main printing processes, and inks are designed for the specific process. Lithography and letterpress are collectively known as the 'paste ink' processes and use inks that are essentially non-volatile at normal temperatures. Flexography and gravure are known as the 'liquid ink' processes and are based upon volatile solvents that evaporate readily at room temperatures. Screen printing uses inks that fall between the other two groups.

Choice of the vehicle (solvent with resins) for a printing ink depends on the printing process, how the ink will be dried, and the substrate on which the image is to be printed. In lithography and letterpress, where inks are dried by absorption and oxidation, vehicles are generally mixtures of mineral and vegetable oils and resins. Flexographic inks, which are designed to dry quickly by evaporation, can be either water-based or based on organic solvents (such as ethanol, ethyl acetate, *n*-propanol or isopropanol) with a wide variety of resins. Vehicles for gravure inks, which also dry by evaporation, may also contain aromatic or aliphatic hydrocarbons and ketones as solvents. Inks for screen printing use organic solvents that are somewhat less volatile than those used for flexography or gravure (higher glycol ethers and aromatic and aliphatic hydrocarbons). Additives in inks include driers, waxes and plasticizers.

Ultraviolet radiation-cured inks, commonly based on acrylates, are used in all of the printing processes to varying degrees.

The manufacture of inks consists of dissolving or dispersing resins in organic solvents or oils to produce the vehicle (varnish), mixing and dispersing the pigment or dye into the vehicle, introduction of any additives and packaging. Some or all of these stages may be done manually or automatically in a batch process or as a continuous process.

During the manufacture of printing inks, exposure to pigments, vehicles and additives can occur through inhalation or skin contact during mixing and dispersion and during clean-up of mixers. Exposures are higher with liquid inks than with paste inks. During newspaper printing by letterpress or lithography, the major exposure is to ink mist. Rotary letterpress was the dominant process for the production of newspapers until the 1970s. It has now been largely replaced by web offset litho, in which exposures to ink mist are considerably lower than for letterpress. In other lithographic and letterpress printing, the major exposure is to hydrocarbon-based cleaning solvents and isopropanol from damping solutions. In flexographic, gravure and screen printing, exposures are mainly to organic solvents. Historically, some workers in both ink manufacture and printing were exposed to much higher levels of lead, polycyclic aromatic hydrocarbons and benzene than today, and the development and use of modern control technologies have made possible the marked reduction in solvent and ink mist exposures.

5.2 Human carcinogenicity data

A large volume of epidemiological data deals with potential cancer risks in printing processes. Because of the presence of a fairly large number of adequate cohort and case-control studies, it was considered that there was no marginal benefit in considering further the descriptive studies based on simple tabulations of death certificate causes of death and mentions of occupation. In any case, these latter studies did not provide clear patterns of results.

The evaluation of results of case-control and cohort studies, in particular those regarding relatively rare neoplasms, was hampered by the possibility of reporting or publication bias. A second problem was the poor specificity of exposure information. While most studies were based on crude designations of the exposure variable, a few, most notably some of the cohort studies, did describe risks for subgroups of the printing industry that are more homogenous in exposure circumstances. The Working Group tried to identify such subgroup studies with presumably more well-defined common exposure circumstances. In a small number of studies, there was an explicit attempt to identify a group of workers exposed to printing inks. This, like the designation of exposure on the basis of the job or industry title, is of poor specificity. Further, most of these were in the context of community-based case-control studies, and the attribution of exposure was based on job-exposure matrices, which do not discriminate among subsectors of the printing industry.

A third problem was that most of the cohort and record-linkage studies had no information on some important confounders, notably cigarette smoking. It has previously been shown that confounding by smoking is unlikely to distort the relative risk estimate between occupation titles and lung cancer by more than 30%. For other sites that are affected by smoking, the maximal bias is likely to be even lower. The Working Group considered these possible biases when interpreting results.

Apart from cancers of the lung, oropharynx, urinary bladder and kidney and leukaemia, which are presented below, the Working Group considered that the findings are not strong or consistent enough to be evaluated.

Lung cancer

Ten community-based case-control studies examined the relationship between lung cancer and occupation and reported results regarding printing industry and/or printing related occupations. Increased relative risks were found in eight studies; smoking was controlled for in six of them and the smoking-adjusted relative risks for 'printing occupations' ranged from 1.1 to 3.3. Two studies reported findings for exposure to printing inks: both found a positive association. A Canadian study found that a small excess of lung cancer detected in printers as a whole was concentrated in printing process workers and was very high for adenocarcinoma of the lung in particular.

Six census-based record-linkage studies reported results for lung cancer. The Swedish study found a statistically significant 60% excess of lung cancer in blue-collar workers in printing enterprises. One study in Denmark showed an increased risk only for women employed in printing, publishing and allied industries. A subsequent Danish study revealed a slight, statistically significantly increased risk in printing and bookbinding industry workers; the risk was higher and still significant in workers employed in newspaper and magazine production. The Finnish study and the two Italian studies did not detect a statistically significant increased risk for lung cancer related to printing occupations.

Among the industry-based studies, five proportionate mortality studies evaluated the risk for lung cancer. In one study, statistically significantly increased risks were found among printing trade workers in two different areas of the United Kingdom. A subsequent, partially overlapping study in London, United Kingdom, reported a statistically significant 30% excess of lung cancer among newspaper printing workers. A third study examined United States newspaper and commercial pressmen separately; neither newspaper nor commercial pressmen showed an increased mortality from lung cancer. The other two proportionate mortality studies in printing workers in the United States failed to show an increased risk for lung cancer.

Among the industry-based studies, seven standardized mortality ratio studies examined lung cancer risk in printing trade workers. Respiratory cancer was elevated in four studies; in none was smoking controlled. An

increased risk for lung cancer was found in the Italian cohort of newspaper workers. The historical cohort of trade union members in the United Kingdom printing industry had a statistically significantly increased risk for lung cancer among mainly unskilled workers in newspaper letterpress printing (machine assistants). Newspaper web pressmen in Los Angeles, United States, showed a nonsignificantly increased lung cancer risk. A Swedish study of rotogravure printers revealed increased risk from respiratory cancers.

In addition, in a cohort of United States Army veterans, an increased smoking-adjusted relative risk for respiratory cancer was found in 'printing pressmen and plate printers'.

In some studies, it was possible to separate newspaper printing workers from other less-well defined employment in the printing industries. Seven cohort studies examined lung cancer risk in workers employed in the newspaper printing industry, mainly during the period 1945-1970. Three were proportionate mortality studies, two of United Kingdom newspaper printing companies and one that examined United States newspaper pressmen and commercial pressmen separately. Four were standardized mortality ratio studies of newspaper web pressmen in Los Angeles, United States, of newspaper printers in two plants in New York City, United States, of newspaper workers in one Italian plant and of newspaper machine assistants who were trade union members in the printing industry in the United Kingdom. Five of the seven cohort studies reported increased relative risk estimates ranging from 1.2 to 1.5, of which three were statistically significant. In none of them was smoking taken into account. In addition, a Danish record-linkage study found a two-fold, statistically significantly increased risk for workers in newspaper and magazine production whose typical job was the operation of rotary letterpress machines.

Cancer of the oropharynx

The risk for cancer of the buccal cavity and pharynx was examined in three case-control studies in the United States. One study on multiple cancer sites showed a smoking-adjusted elevated risk in printing workers. Another similar study detected a significantly high smoking- and alcohol-adjusted risk for cancer of the oral cavity in workers in the printing and publishing industry. A third case-control study on oropharyngeal cancer did not find an increased risk among men employed in the printing industries, whereas a nonstatistically significantly increased risk was found for women. A nonstatistically significantly increased risk was found in male workers in printing and bookbinding industries in a Danish record-linkage study.

Four cohort studies reported results for cancer of the buccal cavity and pharynx. The United States study that examined separately newspaper pressmen and commercial pressmen found a higher than two-fold statistically significantly increased risk in newspaper pressmen only. Increased risks were not found in a standardized mortality ratio study of newspaper pressmen in Los Angeles nor in a cohort of newspaper printers in two plants in New York City. The cohort of trade union members in the United Kingdom printing industry found increased risks in non-production workers (editorial and clerical staff) only.

Urinary bladder cancer

Thirty-five studies have reported findings for urinary bladder cancer and employment in the printing industry. A positive association between urinary bladder cancer and either a printing occupation or employment in the printing industry was reported in 14 of the 23 case-control studies. The range of relative risk estimates derived from these studies was from 1.1 to 5.6. These associations were statistically significant in only three of the case-control studies. Generally, the interpretation of the case-control studies was limited by their use of broad job and industry categories such as printers or the printing industry. One study in Spain reported a nonsignificantly increased relative risk for typesetters and linotypists.

Six cohort studies and six record-linkage studies have also been reported. Increased rate ratios were reported in five of the cohort studies of workers in the printing industry. However, the rate ratios in two of them were close to 1.0 and a statistically significant increase was found only for printing pressmen and plate printers in the cohort of United States Army veterans. Similarly, the relative risk estimates derived from the record-linkage studies were close to unity and the only ones that achieved statistical significance were from the two Danish studies: one study found an increased risk among men employed in printing and bookbinding industries and the other among men employed in printing, publishing and allied industries. Five case-control studies reported

results for exposure to printing inks and urinary bladder cancer risk was observed to be elevated in all five studies.

Cancer of the kidney

Slight to moderate excesses of cancer of the kidney have been reported in the printing industry in five industry-based studies in different cohorts in the United States, and in two record-linkage studies in Italy and Sweden. Ten cohort studies did not report results for cancer of the kidney at all. Four case-control studies, one nested in a cohort of paperboard printing workers and three representing different populations in three continents reported odds ratios ranging from 1.3 to 16.6. Most of these were not statistically significant. By far the most powerful case-control study, a multicentric study conducted in Australia, Denmark, Germany, Sweden and the United States, reported a 30% nonsignificant excess associated with employment in printing and graphic industry.

Leukaemia

Results regarding leukaemia risk in printing workers have been reported in one case-control study and seven cohort studies. The case-control study found a nonstatistically significantly increased risk for printers. Significantly increased risks were found in two cohort studies.

The proportionate mortality study that examined newspaper pressmen and commercial pressmen separately found a 60% excess of leukaemia risk only in newspaper pressmen. In another proportionate mortality study in printing workers in the United States, a statistically significantly increased risk for leukaemia was detected primarily among bindery workers who may have had exposure to benzene. Newspaper web pressmen in Los Angeles, United States, also showed a higher than two-fold increased risk. A Swedish study of rotogravure printers revealed an increased risk for leukaemia, although this was based on a very small number of cases. Both newspaper web pressmen and rotogravure printers may have been exposed to benzene and other organic solvents in the past. Three other cohort studies in newspaper printing workers in London, United Kingdom, commercial pressmen in the United States and newspaper printers in New York City failed to show an increased risk.

Overall, notwithstanding the variability in the results, there are indications of excess risks among printing process workers for some types of cancer. In its evaluation of these data, the Working Group considered the likelihood of publication bias, the possibility of confounding by cigarette smoking, and the imprecision and inconsistency of the designation of exposure groups. Based on these considerations, the Working Group concluded that there is weak evidence of an increased risk of lung and urinary bladder cancers among workers in the printing industry.

While there was a suggestion of an increased risk of lung and urinary bladder cancers in relation to exposure to printing inks, the quality of the data was weak.

The Working Group noted that the vast majority of epidemiological studies covered workers who were in the printing industry in North America or Europe during the middle of the twentieth century. Very few of the studies included workers whose employment was after 1980. Given the rapid technological changes that have gone on in this industry in North America and Europe in the past decade, it is questionable whether the exposure circumstances that were prevalent in the past are still prevalent. However, there may be areas of the world in which the older processes are still prevalent. Where the technologies have substantially changed from those of the past and insofar as this has changed the exposure conditions, the present evaluation may not be relevant.

5.3 Animal carcinogenicity data

Twenty-two different printing inks were tested for carcinogenicity in one study in mice by subcutaneous injection. The study was inadequate for evaluation.

5.4 Other relevant data

No consistent association between employment in printing trades and morbidity from non-malignant diseases has been observed. Solvent-induced central nervous system damage has been observed in several but not all studies on employees in printing trades. Ultraviolet radiation-cured printing inks are a frequent cause of allergic contact dermatitis.

One study suggested that occupational exposures may induce hepatic damage in printers, but several other studies failed to confirm this finding.

An early report of an increased risk of anencephalus associated with paternal employment in printing has not been confirmed in subsequent studies of neural tube defects. In two studies, an association between this exposure and cleft lip and/or palate has been observed. However, in one of these, the association was apparent only for cleft palate, and in the other only for cleft lip, and no noteworthy association has been observed in a further three studies. In a single study in rats, dermal exposure to newspaper inks had no effect on sperm numbers or motility, vaginal cytology or oestrus cycle length.

Several pigments and dyes used in printing inks are mutagenic in *Salmonella typhimurium*: para red, dinitroaniline orange, azo dye D & C Red No. 9.

An increased frequency of chromosomal aberrations in peripheral lymphocytes in printing workers exposed to *inter alia* toluene was found in two studies, but not in two other studies. In one study, an increased frequency of chromosomal aberrations was found in workers exposed to toluene and benzene. In one study of a group exposed to toluene, an increased frequency of sister chromatid exchange was found, but not in two other studies. In one study of printers exposed to lead, increased frequencies of chromosomal aberrations and sister chromatid exchange were found. In one study, an increased frequency of micronuclei was observed in printing workers exposed to toluene. In one study of volunteers exposed to toluene, no increase in sister chromatid exchange was observed in lymphocytes.

5.5 Evaluation

There is *limited evidence* that occupational exposures in printing processes are carcinogenic.

There is *inadequate evidence* for the carcinogenicity in humans of printing inks.

There is *inadequate evidence* for the carcinogenicity in experimental animals of printing inks.

Overall evaluation

Occupational exposures in printing processes are *possibly carcinogenic to humans (Group 2B)*.

Printing inks are *not classifiable as to their carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

CARBON BLACK (Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 65 (1996) (p. 149)

CAS No.: 1333-86-4

Chem. Abstr. Names:

- Carbon black, acetylene
- Carbon black, channel
- Carbon black, furnace
- Carbon black, lamp
- Carbon black, thermal

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Carbon black is a powdered form of elemental carbon manufactured by the vapour-phase pyrolysis of hydrocarbon mixtures, such as heavy petroleum distillates and residual oils, coal-tar products, natural gas and acetylene. Worldwide production of carbon black in 1993 was approximately 6 million tonnes.

Carbon blacks are categorized as acetylene black, channel black, furnace black, lampblack or thermal black, according to the process by which they are manufactured. Lampblack is the oldest type of carbon black, having been used as a pigment for centuries. Channel black, produced from natural gas, was introduced in the late nineteenth century and was the major carbon black used worldwide in the early twentieth century for rubber and pigment applications; with the exception of a special product made in Germany, it is no longer produced. Acetylene, furnace and thermal blacks have been produced since the early twentieth century. Over 90% of all carbon black produced today is furnace black.

The primary use of carbon black is in rubber products, mainly tyres and other automotive products, but also in many other rubber products such as hoses, gaskets and coated fabrics. Much smaller amounts of carbon black are used in inks and paints, in plastics and in the manufacture of dry-cell batteries.

Types of carbon black are characterized by the size distribution of the primary particles, the degree of their aggregation and agglomeration and the various chemicals adsorbed onto the surfaces. Average primary particle diameters in several commercially produced carbon blacks range from 10 to 400 nm, while average aggregate diameters range from 100 to 800 nm. Typical classes of chemicals adsorbed onto the carbon black surface are polycyclic aromatic hydrocarbons (PAHs), nitro derivatives of PAHs and sulfur-containing PAHs. Examples of PAHs extracted most frequently from carbon black using a variety of extraction methods (e.g. prolonged Soxhlet extraction with benzene or toluene) include benzopyrenes, benzo[ghi]perylene, coronene, fluoranthene and pyrene.

Exposures to carbon black vary markedly within any production facility. The highest levels of exposure are experienced by those who interact with the process the most, including fitters/welders, warehouse packers and site cleaners. Exposures can vary greatly among factories and regionally.

Several studies in the 1960s found very high levels of exposure, even up to 1000 mg/m³ in furnace, lamp- and channel black plants. Later studies in some countries have found lower levels, although many of these were in

excess of the existant occupational exposure limits. In the late 1980s and early 1990s, more extensive studies in western Europe and the United States have found (geometric mean) personal exposure to total inhalable carbon black to be on average less than 1 mg/m³. Even lower exposures may occur among some workers in industries using carbon black, such as rubber, printing ink and paint manufacture, and exposures to carbon black in the use of rubber, printing ink or paint are negligible.

5.2 Human carcinogenicity data

The greatest potential for elucidating the carcinogenicity of carbon black is in the carbon black production industry where carbon black has been the prime industrial exposure and where exposure levels have been high. Cohort studies of carbon black production workers have been conducted in the United States and in the United Kingdom. Interpretation of the study in the United States is hampered by problems of uncertainty in the completeness of the cohort and in the definition and completeness of follow-up. The study in the United Kingdom also had some problems in completeness of the cohort, but the follow-up was probably complete. In both cohorts, fewer observed than expected deaths due to all causes occurred and, in the study in the United States, this may in part have been attributable to under-ascertainment of deaths or to inflation of person-years of follow-up. The study in the United States found no excess mortality due to any type of cancer when compared to state vital statistics rates; in fact there were deficits for some types of cancer. The study in the United Kingdom found an excess of respiratory cancer deaths (standardized mortality ratio, 1.5; 95% confidence interval, 1.0-2.2).

A nested case-control study within the United States cohort was hampered by very small numbers and problems of interpretation. Most cases were of non-melanoma skin cancer. Neither for all cancers combined nor for skin cancers alone was there evidence that cases had higher cumulative exposure to carbon black than controls.

A cohort study was carried out among workers in the United States to assess cancer risks due to exposure to formaldehyde. Ten participating plants were spread across several industries in which workers may have experienced exposure to formaldehyde. To control for confounding and modification of effect by other exposures, workers' exposures to various other chemicals, including carbon black, were assessed by industrial hygienists. For all assessed levels and durations of exposure to carbon black combined, there was a slight nonsignificant excess of lung cancer. There was no clear trend by duration of exposure. Carbon black-exposed workers in this cohort may also have been exposed to formaldehyde and other substances.

Another industry-based study was a nested case-control study conducted in the tyre and rubber manufacturing industry to examine the association of squamous-cell carcinoma of the skin with rubber manufacturing materials. For each study subject, industrial hygienists assessed exposure to five substances, including carbon black, based on evaluations of each subject's job history. The results of this study indicated no effect of carbon black on skin cancer.

In a community-based case-control study in Canada, interviews were designed to obtain detailed lifetime job histories and information on potential confounders. Potential occupational exposures were identified for each job description, and among the exposures assessed was carbon black. In this study population, potential exposure to carbon black occurred in some individuals in user industries, notably among painters and in the printing and rubber industries. For the following cancer sites, there was no indication of excess risk in relation to carbon black: stomach, colon, rectum, pancreas, prostate, urinary bladder, skin melanoma and non-Hodgkin's lymphoma. For the following sites there was indication of excess risk: oesophagus, kidney and lung. The lung cancer excess was particularly concentrated among oat-cell cancers.

A Swedish case-control study reported a nonstatistically significantly increased risk for urothelial cancer for men exposed to carbon black.

In assessing all the available data, there is no evidence of an effect of carbon black for most cancer sites. For cancers of the urinary bladder, kidney and oesophagus, isolated results indicate excess risks, but these are not sufficient to support an evaluation of human carcinogenicity.

Two studies were informative for non-melanoma skin cancer (a nested case-control study among the United States carbon black production cohort and a nested case-control study among rubber workers); neither demonstrated any excess risk for skin cancer due to carbon black.

Of the studies listed above, four were considered informative for lung cancer. Of those, two indicated excess risk among carbon black-exposed workers at borderline statistical significance (the carbon black production cohort in the United Kingdom and the Canadian community-based study), one indicated excess risk but was not significant (the United States formaldehyde cohort) and the other indicated no excess (the United States carbon black production cohort).

Each of the available studies has limitations for the specific purpose of assessing the carcinogenicity of carbon black. The Working Group considered the study of carbon black producers in the United Kingdom to be the most informative for this purpose. That study indicated an excess risk of borderline significance. Confounding by smoking could not be excluded, although some information was presented indicating that it was unlikely. The formaldehyde cohort study indicated a slight excess of lung cancer among the subgroup exposed to carbon black, but this could easily have been due to chance or confounding by formaldehyde or other occupational substances. The community-based study in Montréal of exposure in a variety of user industries showed an elevated risk in the subgroup categorized as having high exposure to carbon black; the result was of borderline statistical significance using a cancer series control group and not significant using a population control group. It is not clear which control group provides the most valid estimates. Even the high-exposure subgroup of this study was unlikely to have experienced exposure levels of the same order of magnitude as did workers in the carbon black production industry. Although the United States carbon black worker study, which was negative, was large, its methodological limitations detracted from its value. The Working Group therefore considered the whole body of evidence rather weak and the results conflicting.

5.3 Animal carcinogenicity data

No adequate study of the carcinogenicity of carbon black administered by the oral route was available.

In one study in female mice by inhalation exposure, carbon black did not increase the incidence of respiratory tract tumours.

Two different carbon black products were tested in two inhalation studies in female rats and in one study using rats of each sex. Significant increases in the incidence of malignant lung tumours and the incidence of benign and malignant lung tumours combined were observed in female rats in all three studies. In addition, increased incidences of lesions described as benign cystic keratinizing squamous-cell tumours or squamous cysts were observed.

In two studies in female rats by intratracheal administration, using one type of carbon black, both extracted and non-extracted material increased the incidence of benign and malignant lung tumours. In one of the studies, a different type of extracted carbon black with a larger primary particle size increased the incidence of lesions described as benign cystic keratinizing squamous-cell tumours.

In several skin-painting studies in mice using various carbon blacks, no carcinogenic effect on the skin was observed; the painting of several carbon black extracts (benzene extracts) resulted in skin tumours.

In a series of studies in male and female mice by subcutaneous injection, a carbon black containing demonstrable quantities of carcinogenic PAHs produced local sarcomas, whereas a carbon black from which no PAH was detected did not produce such sarcomas. In several studies in mice, solvent extracts of carbon black produced sarcomas following subcutaneous injection.

5.4 Other relevant data

Upon inhalation exposure of humans to carbon black, these particles are deposited in the lung. The exposure

may cause slight radiological changes. The prevalence of radiological findings has varied considerably among different studies, probably because of varying radiological techniques and possibly also due to different exposure circumstances and possible concomitant exposures to other compounds. Further, workers may develop chronic bronchitis and a slight reduction in lung function. These findings may be interpreted mainly as a slight nonspecific irritant effect of heavy dust exposure. On the other hand, some data indicate a fibrous tissue reaction in the area surrounding the carbon deposits in the lung parenchyma.

Studies on the pulmonary retention of inhaled carbon blacks in rats and mice have shown that these particles behave very similarly to other low-solubility, low-toxicity particles. Carbon black displayed normal retention characteristics in rats at lung burdens not exceeding a certain level which is approximately in the range of 0.5-1 mg/g of lung. At higher lung burdens, a prolonged clearance is found. Impaired particle clearance due to high loading of carbon black in experiments with rats results in increased accumulation of particles. Subsequent inflammatory responses occur which develop into chronic active inflammation. Increased collagen deposition from proliferating fibroblasts, increased epithelial cell proliferation and metaplasia have been found at high lung burdens of carbon black. It appears that the high specific surface area of most carbon blacks may be an important parameter in the induction of inflammatory and subsequent other responses in the lung. One study with carbon black in rats confirmed findings with other particles that females are more sensitive than males.

Most assays for mutagenicity are negative for carbon black. In rats exposed to carbon black by inhalation, *hprt* mutant frequency was elevated in type II cells following a 12-week exposure. Carbon black did not induce a significant increase in DNA adducts in peripheral lung tissue of rats after two years of inhalation exposure. In another study, exposure of rats by inhalation to carbon black increased DNA adduct levels in type II cells. K-*ras* mutations were found in one out of 18 neoplasms analysed from a carbon black-exposed rat. No exposure-related *p53* mutation was found.

Some mechanistic considerations on particle-induced lung neoplasms are presented.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of carbon black.

There is *sufficient evidence* in experimental animals for the carcinogenicity of carbon black.

There is *sufficient evidence* in experimental animals for the carcinogenicity of carbon black extracts.

Overall evaluation

Carbon black is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Previous evaluation: Suppl. 7 (1987) (p. 142)

Synonyms:

Synonyms for carbon black, acetylene

- Acetylene Black
- CI 77266
- CI Pigment Black 7
- Explosion acetylene black
- Explosion black
- P68

- P1250
- Shawinigan acetylene black
- Ucet

Synonyms for carbon black, channel

- Aroflow
- Arrow
- Atlantic
- Black Pearls
- Carbolac
- Carbomet
- Channel black
- CI 77266
- CI Pigment Black 7
- CK3
- Collocarb
- Conductex, Continental
- Croflex
- Crolac
- Degussa
- Dixie
- Dixiecell
- Dixiedensed
- Elf
- Excelsior
- Farbruss
- Fecto
- Huber
- Impingement black
- Kosmink
- Kosmobil
- Kosmolak
- Kosmos
- Kosmovar
- Micronex
- Mogul
- Monarch
- Neo-Spectra
- Peerless
- Printex
- Raven
- Regent
- Royal Spectra
- Special Black IV & V
- Spheron
- Superba
- Super-Carbovar
- Super-Spectra
- Texas
- Triangle
- United
- Witco
- Wyex

Synonyms for carbon black, furnace

- Aro
- Arogen
- Aromex
- Arotone
- Arovel
- Atlantic
- Black Pearls
- Carbodis
- CI 77266
- CI Pigment Black 7
- Collocarb
- Conductex, Continex
- Corax
- Croflex
- Dixie
- Durex
- Elftex
- Essex
- Furnace black
- Furnal
- Furnex
- Gas-furnace black
- Gastex
- Huber
- Humenegro
- Kosmos
- Metanex
- Modulex
- Mogul
- Molacco
- Monarch
- Neotex
- Oil-furnace black
- Opal
- Peerless
- Pelletex
- Philblack
- Printex
- Rebonex
- Regal
- Special Schwarz
- Statex
- Sterling
- Texas
- Ukarb
- United
- Vulcan

Synonyms for carbon black, lamp

- Carbon Black BV and V
- CI 77266
- CI Pigment Black 6
- Durex
- Eagle Germantown
- Flamruss
- Lamp black
- Magecol

- Tinolite
- Torch Brand

Synonyms for carbon black, thermal

- Atlantic
- Cancarb
- CI 77266
- CI Pigment Black 7
- Croflex
- Dixitherm
- Huber
- Kosmotherm
- Miike 20
- P-33
- Sevacarb
- Shell Carbon
- Statex
- Sterling
- Therma-atomic black
- Thermal black
- Thermatomic
- Thermax
- Thermblack
- Velvetex

Last updated 08/14/1997

2-CHLORONITROBENZENE, 3-CHLORONITROBENZENE AND 4-CHLORONITROBENZENE (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 65 (1996) (p. 263)

CAS No.: 88-73-3

Chem. Abstr. No.: 1-Chloro-2-nitrobenzene

CAS No.: 121-73-3

Chem. Abstr. No.: 1-Chloro-3-nitrobenzene

CAS No.: 100-00-5

Chem. Abstr. No.: 1-Chloro-4-nitrobenzene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

2-, 3- and 4-Chloronitrobenzenes are produced as a mixture by nitration of chlorobenzene. After separation, the three isomers are used as important chemical intermediates in the production of colourants, pharmaceuticals and a variety of other products. Human exposure to chloronitrobenzenes may occur during the production and use of these intermediates.

5.2 Human carcinogenicity data

No data on the carcinogenicity of 2-, 3- or 4-chloronitrobenzene to humans were available to the Working Group.

5.3 Animal carcinogenicity data

2-Chloronitrobenzene was tested for carcinogenicity by oral administration in the diet in one study in mice and in one study in rats. The studies were inadequate for an evaluation. 4-Chloronitrobenzene was tested for carcinogenicity by oral administration in the diet in one study in mice and in one study in rats. Although the study in mice reported an increased incidence of vascular tumours in exposed males and females, neither study was considered adequate for an evaluation. 3-Chloronitrobenzene has not been tested for carcinogenicity in experimental animals.

5.4 Other relevant data

4-Chloronitrobenzene is absorbed through inhalation and/or via the skin upon human exposure after which urinary metabolites of 4-chloronitrobenzene appear, which are the results of *N*-acetylation, nitro-group reduction and — to a lesser extent — ring-hydroxylation. Metabolism is slow, with elimination of metabolites occurring over many days. Considerable interindividual variation occurs in this metabolism.

The urinary metabolites of 4-chloronitrobenzene are qualitatively similar in humans and rats.

No data concerning the absorption, distribution, metabolism and excretion or toxic effects of 2- or 3-chloronitrobenzene in humans were available to the Working Group.

The disposition of 2-chloronitrobenzene in rats is similar to that of 4-chloronitrobenzene.

In humans, exposure to 4-chloronitrobenzene is associated with such symptoms as headache, palpitation, dizziness, nausea, vomiting and poor appetite. Cyanosis, methaemoglobinaemia and anaemia also occur. Methaemoglobinaemia and anaemia occur in rats exposed to 4-chloronitrobenzene, 3-chloronitrobenzene or 2-chloronitrobenzene.

In a single study in rats, a maternally toxic dose of 4-chloronitrobenzene increased the resorption rate and the frequency of skeletal malformations. In female rats and mice, inhalation exposure to 4-chloronitrobenzene increased the oestrus cycle length. In rats, but not mice, inhalation exposure to the compound decreased spermatogenesis with atrophy of the seminiferous tubules. In a continuous breeding study, a progressive decrease in fertility was noted in mice receiving 4-chloronitrobenzene.

In rats and mice exposed to 2-chloronitrobenzene by inhalation, decreased spermatogenesis was observed. No significant change was observed in exposed females. In a continuous breeding study, fertility was not affected in mice receiving 2-chloronitrobenzene.

2-Chloronitrobenzene induced reverse mutations but not primary DNA damage in bacteria. It was not mutagenic to insects. In mammalian cells *in vitro*, it induced sister chromatid exchange and chromosomal aberrations. Intraperitoneal injection into mice resulted in DNA damage in the liver, kidney and brain.

3-Chloronitrobenzene gave negative results in bacterial mutagenicity assays and in cultured mammalian cell chromosomal assays.

4-Chloronitrobenzene induced reverse mutations but not primary DNA damage in bacteria. It was not mutagenic to insects. At toxic doses, it induced chromosomal aberrations, sister chromatid exchange and repairable DNA breaks in cultured mammalian cells. Intraperitoneal injection into mice induced DNA damage in the liver, kidney and brain.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of chloronitrobenzenes.

There is *inadequate evidence* in experimental animals for the carcinogenicity of chloronitrobenzenes.

Overall evaluation

Chloronitrobenzenes are *not classifiable as to their carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#)

Synonyms for 2-Chloronitrobenzene

- *ortho*-Chloronitrobenzene
- 2-Chloro-1-nitrobenzene
- 2-CNB
- *ortho*-Nitrochlorobenzene
- 1-Nitro-2-chlorobenzene

Synonyms for 3-Chloronitrobenzene

- 3-Chloro-1-Nitrobenzene
- *meta*-Chloronitrobenzene
- 3-CNB
- 1-Nitro-3-Chlorobenzene
- *meta*-Nitrochlorobenzene

Synonyms for 4-Chloronitrobenzene

- *para*-Chloronitrobenzene
- 4-Chloro-1-nitrobenzene
- 4-CNB
- 4-Nitrochlorobenzene
- *para*-Nitrochlorobenzene
- 1-Nitro-4-chlorobenzene
- 4-Nitro-1-chlorobenzene
- *para*-Nitrophenyl chloride

Last updated 08/14/1997

3,7-DINITROFLUORANTHENE AND 3,9-DINITROFLUORANTHENE (Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

Vol.: 65 (1996) (p. 297)

CAS No.: 105735-71-5

Chem. Abstr. Name: 3,7-Dinitrofluoranthene

CAS No.: 22506-53-2

Chem. Abstr. Name: 3,9-Dinitrofluoranthene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

3,7- and 3,9-Dinitrofluoranthenes are produced for laboratory use by nitration of fluoranthene. 3,7- and 3,9-Dinitrofluoranthenes have been detected at low levels in emissions from diesel engines, kerosene heaters and other combustion sources.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

3,7- and 3,9-Dinitrofluoranthenes were tested for carcinogenicity in rats by subcutaneous injection in one study and by pulmonary implantation in another study. Subcutaneous injection of 3,7- and 3,9-dinitrofluoranthenes induced a high incidence of subcutaneous tumours at the site of injection, most of which were malignant fibrous histiocytomas. Pulmonary implantation of 3,7- and 3,9-dinitrofluoranthenes induced a high incidence of lung tumours, most of which were squamous-cell carcinomas.

5.4 Other relevant data

3,7- and 3,9-Dinitrofluoranthenes are highly mutagenic to bacteria, particularly in the absence of an exogenous metabolic system. In mammalian cells *in vitro*, these compounds induced chromosomal aberrations but not gene mutations. *In vivo*, they induced micronuclei in mouse bone marrow.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 3,7- and 3,9-dinitrofluoranthenes.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 3,7- and 3,9-dinitrofluoranthenes.

Overall evaluation

3,7- and 3,9-Dinitrofluoranthenes are *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see [Preamble Evaluation](#)

Previous evaluation

3,7-Dinitrofluoranthene: Vol. 46 (1989) (p. 189)

3,9-Dinitrofluoranthene: Vol. 46 (1989) (p. 195)

Last updated 08/14/1997

**2,4-DINITROTOLUENE, 2,6-DINITROTOLUENE
AND 3,5-DINITROTOLUENE
2,4- and 2,6-Dinitrotoluenes (Group 2B)
3,5-Dinitrotoluene (Group 3)**

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 65 (1996) (p. 309)

CAS No.: 25321-14-6

Chem. Abstr. Name: Dinitrotoluene

CAS No.: 121-14-2

Chem. Abstr. Name: 1-Methyl-2,4-dinitrobenzene

CAS No.: 606-20-2

Chem. Abstr. Name: 2-Methyl-1,3-dinitrobenzene

CAS No.: 618-85-9

Chem. Abstr. Name: 1-Methyl-3,5-dinitrobenzene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

2,4-, 2,6- and 3,5-Dinitrotoluenes are produced by nitration of toluene or nitrotoluenes. Dinitrotoluenes are used primarily as chemical intermediates in the production of toluene diamines and diisocyanates (mainly as the mixture of 2,4- and 2,6-isomers), while smaller amounts of the three isomers are also used to produce dyes, explosives and propellants. Human exposure to dinitrotoluenes can occur by inhalation or skin absorption during their production and use as intermediates. They have been detected in wastewater from dinitrotoluene production and use, and in surface and groundwater in the vicinity of these manufacturing facilities.

5.2 Human carcinogenicity data

A cohort study of workers from a munitions factory in the United States found an increased risk for cancer of the liver and gall-bladder among workers exposed to a mixture of 2,4- and 2,6-dinitrotoluenes, based on six cases. No such increase was detected in a previous study based on a smaller group of workers from the same and another munitions factory in the United States. These findings were not considered to be strong or consistent enough to permit a conclusion on the carcinogenicity of dinitrotoluenes in humans.

5.3 Animal carcinogenicity data

2,4-Dinitrotoluene was tested by oral administration in two adequate studies in mice and two adequate studies in rats. In one study in mice, no tumorigenic effect was reported. In the second study in mice, using higher doses, tumours of the renal tubular epithelium were observed in males. In both studies in rats, the incidence of various tumours of the integumentary system was increased in males. The incidence of hepatocellular carcinomas was increased in treated males and females in one study. The incidence of fibroadenomas of the mammary gland was increased in females in both studies.

2,6-Dinitrotoluene was tested for carcinogenicity by oral administration in two studies in male rats and

increased the incidence of hepatocellular neoplastic nodules and carcinomas.

3,5-Dinitrotoluene has not been tested for carcinogenicity in experimental animals.

Technical-grade dinitrotoluene (approximately 80/20 2,4/2,6-isomers) was tested for carcinogenicity in two studies in rats by oral administration producing hepatocellular neoplastic nodules and hepatocellular carcinomas in male rats in one study and in both sexes in a second study.

5.4 Other relevant data

Dinitrotoluenes are absorbed following dermal and inhalation exposure of workers.

The most abundant metabolites of dinitrotoluenes found in urine from exposed workers were dinitrobenzoic acids. In addition, amino metabolites have been reported. The appearance of reduced metabolites suggests either that human hepatic enzymes are capable of reduction of the nitro group of dinitrotoluene or that dinitrotoluene (or its metabolites) gains access to the intestinal microflora which is capable of reduction, after which the metabolites are reabsorbed and excreted into urine. Limited data indicate a sex difference in humans as regards the urinary metabolite pattern. In humans, the elimination half-life for the urinary metabolites is 1-2.7 h.

The metabolism and excretion of dinitrotoluenes by rats seem to be qualitatively similar to those in humans. However, there are quantitative differences as regards prevalence of different metabolites. Thus, the major urinary metabolites of 2,4-dinitrotoluene are 2,4-dinitrobenzoic acid in humans and 2,4-dinitrobenzyl alcohol in rats.

Heavy human exposure to technical-grade dinitrotoluene may cause a variety of symptoms and signs, including cyanosis - presumably because of methaemoglobinaemia - anaemia and toxic hepatitis. Further, dinitrotoluenes may give rise to allergic contact dermatitis.

A variety of toxic effects are observed in animals following acute administration of various dinitrotoluene isomers. Certain dinitrotoluene isomers, most notably 2,6-dinitrotoluene, produce extensive centrilobular hepatic necrosis following administration *in vivo*.

In laboratory animals, the chronic toxic effects following exposure to dinitrotoluene include various neurotoxic effects (including paralysis), hepatotoxicity, including dysplasia, hyperplastic foci and hepatic megalocytosis, anaemia and methaemoglobinaemia.

No association was found between exposure to the compounds of male workers in a dinitrotoluene facility and the results of semen analysis, the levels of follicle-stimulating hormone or the occurrence of miscarriages or delayed conception in their partners.

In female rats, administration of technical-grade dinitrotoluene by gavage did not produce teratogenic effects even at dose levels which produce significant maternal and embryo/fetal toxicity. In studies in male rats, 2,4-dinitrotoluene induced adverse reproductive effects and anti-spermatogenic activity.

No data on the metabolism or toxicity of 3,5-dinitrotoluene were available to the Working Group.

2,4-Dinitrotoluene (technical grade) is weakly mutagenic in bacteria. It was inactive in mammalian cells *in vitro* in tests for gene mutation, unscheduled DNA synthesis and transformation, but inhibited intercellular communication at toxic concentrations. In rats *in vivo*, it induced unscheduled DNA synthesis in hepatocytes, provided the normal gut flora was present. It induced sister chromatid exchange in rat lymphocytes exposed *in vivo*. In mice, it was negative in the bone-marrow micronucleus test, the dominant lethal test and the spot test.

Purified 2,4-dinitrotoluene showed DNA binding in rats *in vivo* in several organs, the binding being highest in the liver. Three distinct adducts were identified. In bacteria, it induced DNA damage and gene mutation. In insects, it induced sex-linked recessive lethal mutations but not dominant lethal mutations or translocations. In mammalian cells *in vitro*, it induced DNA strand breaks, gene mutations in mouse lymphoma cells (without activation) but not in Chinese hamster ovary cells and a low frequency of sister chromatid exchange but not of chromosomal aberrations in Chinese hamster ovary cells. It inhibited intercellular communication but did not induce cell transformation. In mammals *in vivo*, 2,4-dinitrotoluene induced a weak response in unscheduled DNA synthesis in rat hepatocytes but was negative in the dominant lethal assay and the sperm morphology test in mice.

2,6-Dinitrotoluene is weakly mutagenic in bacteria. In mammalian cells *in vitro*, it induced DNA strand breaks but not gene mutation or cell transformation. Studies of the inhibition of intercellular communication gave equivocal results. With 2,6-dinitrotoluene, DNA adducts were found after in-vivo exposure of rats. *In vivo*, it induced unscheduled DNA synthesis in rat hepatocytes. In the urine of exposed rats, mutagenic metabolites could be detected.

Experiments indicate the following steps in the metabolic activation leading to the formation of adducts: (1) 2,6-dinitrotoluene is metabolized in the liver; (2) metabolites are excreted in the bile; (3) the biliary metabolites are hydrolysed and further metabolized in the intestine; and (4) after enterohepatic transportation of the metabolites back to the liver, the metabolites are activated further and bound to macromolecules.

3,5-Dinitrotoluene is mutagenic in bacteria but did not induce DNA damage or mutations in mammalian cells in culture.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 2,4-, 2,6- and 3,5-dinitrotoluenes.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 2,4-dinitrotoluene and 2,6-dinitrotoluene.

There is *inadequate evidence* in experimental animals for the carcinogenicity of 3,5-dinitrotoluene.

Overall evaluation

2,4- and 2,6-Dinitrotoluenes are *possibly carcinogenic to humans (Group 2B)*.

3,5-Dinitrotoluene is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonyms for 2,4-dinitrotoluene

- Dinitrotoluene
- 2,4-Dinitrotoluol
- DNT
- 2,4-DNT
- 4-Methyl-1,3-dinitrobenzene

Synonyms for 2,6-dinitrotoluene

- 2,6-DNT

- 1-Methyl-2,6-dinitrobenzene

Synonym for 3,5-dinitrotoluene

- 3,5-DNT

Last updated 08/14/1997

2-NITROANISOLE (Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

Vol.: 65 (1996) (p. 369)

CAS No.: 91-23-6

Chem. Abstr. Name: 1-Methoxy-2-nitrobenzene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

2-Nitroanisole is produced by the reaction of methanolic sodium hydroxide with 2-chloronitrobenzene. It is mainly used in the production of the dye intermediates *ortho*-anisidine and *ortho*-dianisidine. Human exposure may occur during its production and use.

5.2 Human carcinogenicity data

No data on the carcinogenicity of 2-nitroanisole in humans were available to the Working Group.

5.3 Animal carcinogenicity studies

2-Nitroanisole was tested for carcinogenicity by oral administration in one study in mice and in two studies in rats. In mice, the incidence of hepatocellular adenomas was increased in males and females, and that of hepatoblastomas was increased in males. In one study in rats, the incidence of mononuclear-cell leukaemia was increased in males and females. In the second study, which used a shorter duration of treatment but higher doses, increases were seen in the incidences of tumours of the urinary bladder, the large intestine and the kidney.

5.4 Other relevant data

No human data were available on the metabolism of 2-nitroanisole.

In rats, 2-nitroanisole is absorbed after oral administration, and the major route of its rapid elimination is the urine. The predominant metabolic pathway involves the formation of 2-nitrophenol, with its subsequent conjugation with sulfate and glucuronic acid. 2-Nitroanisole causes methaemoglobinaemia following dietary administration of high doses to rats and mice. Pathological lesions observed in rats occurred in the urinary bladder, spleen, kidney and liver. In mice, 2-nitroanisole causes hypertrophy in the liver.

2-Nitroanisole is mutagenic in bacteria. In single studies, it induced mutations, sister chromatid exchange and a low frequency of chromosomal aberrations in cultured mammalian cells.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 2-nitroanisole.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 2-nitroanisole.

Overall evaluation

2-Nitroanisole is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonyms

- 2-Methoxynitrobenzene
- 2-Methoxy-1-nitrobenzene
- *ortho*-Nitroanisole
- *ortho*-Nitrobenzene methyl ether
- 2-Nitromethoxybenzene
- *ortho*-Nitromethoxybenzene
- 1-Nitro-2-methoxybenzene
- *ortho*-Nitrophenyl methyl ether

08/14/1997

NITROBENZENE

(Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

Vol.: 65 (1996) (p. 381)

CAS No.: 98-95-3

Chem. Abstr. Name: Nitrobenzene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Nitrobenzene has been produced commercially since the early nineteenth century by nitration of benzene. It is a major chemical intermediate used mainly in the production of aniline, itself a major chemical intermediate in the production of dyes. Human exposure may occur both by inhalation and by skin absorption during its production and use. Nitrobenzene has been detected in surface and groundwater.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Nitrobenzene was tested by inhalation exposure in one study in mice and in two studies in rats. In mice, the incidences of alveolar-bronchiolar neoplasms and thyroid follicular-cell adenomas were increased in males. In one study in rats, the incidences of hepatocellular neoplasms, thyroid follicular-cell adenomas and adenocarcinomas and renal tubular-cell adenomas were increased in treated males. In treated females, the incidences of hepatocellular neoplasms and endometrial stromal polyps were increased. In a study using male rats only, the incidence of hepatocellular neoplasms was increased.

5.4 Other relevant data

In humans, nitrobenzene is readily absorbed by inhalation. Penetration through the skin also occurs. A major part of the absorbed dose is excreted into the urine: 10-20% of the dose is excreted as 4-nitrophenol, the concentration of which may be used for biological monitoring. A smaller fraction is excreted as 4-aminophenol. The elimination kinetics contains at least two compartments, the first with a half-life of hours and the second with a half-life of days.

In rodents and rabbits, 4-nitrophenol and 4-aminophenol are major urinary metabolites.

There is limited information on the toxic effects of exposure to nitrobenzene in humans. However, it is clear that both accidental ingestion and occupational exposure may cause methaemoglobinaemia, haemolytic anaemia and toxic hepatitis.

Following inhalation of nitrobenzene, liver, lung and splenic toxicity is observed in both rats and mice, although mice appear to be more sensitive than rats to the toxic effects of this chemical. Methaemoglobinaemia and anaemia are also observed in both rats and mice.

In female rats, no teratogenic or reproductive effect of exposure to nitrobenzene was observed. Testicular

atrophy has been observed in rats. In a two-generation reproduction study in rats, a decrease in the fertility index of the F0 and F1 generations occurred. No teratogenic effect has been observed in rabbits.

Nitrobenzene was non-genotoxic in bacteria and mammalian cells *in vitro*. In mammals *in vivo*, it was inactive.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of nitrobenzene.

There is *sufficient evidence* in experimental animals for the carcinogenicity of nitrobenzene.

Overall evaluation

Nitrobenzene is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonyms

- Essence of mirbane
- Essence of myrbane
- Mirbane oil
- Nitrobenzol
- Oil of mirbane
- Oil of myrbane

2-NITROTOLUENE, 3-NITROTOLUENE AND 4-NITROTOLUENE (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

VOL.: 65 (1996) (p. 409)

CAS No.: 88-72-2

Chem. Abstr. Name: 1-Methyl-2-nitrobenzene

CAS No.: 99-08-1

Chem. Abstr. Name: 1-Methyl-3-nitrobenzene

CAS No.: 99-99-0

Chem. Abstr. Name: 1-Methyl-4-nitrobenzene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

2-, 3- and 4-Nitrotoluenes are produced commercially, as a mixture, by nitration of toluene. 2- and 4-Nitrotoluenes are used mainly to produce intermediates in the production of colourants. All of these isomers are also used in much smaller quantities in the production of agricultural, pharmaceutical and rubber chemicals. Human exposure to nitrotoluenes can occur during their production and use, although few data are available. Nitrotoluenes have been detected in effluents from the manufacture or use of nitrotoluenes and in surface and groundwater.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

No long-term study of the carcinogenicity of 2-, 3- or 4-nitrotoluene was available to the Working Group.

Rare mesotheliomas of the tunica vaginalis were reported in male rats receiving 2-nitrotoluene in the diet for 13 weeks.

5.4 Other relevant data

No relevant data on absorption, distribution, metabolism or excretion in humans were available to the Working Group.

Urinary elimination is the major route of excretion in rats exposed to nitrotoluene isomers. Male rats excrete more of an administered dose of nitrotoluene in the bile compared with female rats. All three nitrotoluene isomers cause an increase in the incidence of hyaline droplet nephropathy in male rats: the hyaline droplets were associated with 2-globulin. Liver toxicity was observed in rats exposed to 2-nitrotoluene. In mice, the only evidence of toxicity was degeneration and metaplasia of the olfactory epithelium.

In rats, no adverse effect on reproduction or on the offspring was observed following administration of 2-, 3- or 4-nitrotoluene by gavage. All three isomers impaired testicular function and increased the length of the oestrus cycle. The 2-isomer decreased sperm motility in mice.

2-Nitrotoluene was not genotoxic in bacteria, but induced sister chromatid exchange in cultured mammalian cells. *In vivo* in rats, 2-nitrotoluene bound to macromolecules and, in males, induced unscheduled DNA synthesis in liver cells. In-vivo activity depends on the presence of intestinal bacteria.

3-Nitrotoluene produced a weak induction of sister chromatid exchange, but not of chromosomal aberrations or unscheduled DNA synthesis in mammalian cells *in vitro*. *In vivo*, it bound to macromolecules but not to DNA and did not induce unscheduled DNA synthesis.

4-Nitrotoluene was not genotoxic in yeast. In mammalian cells *in vitro*, it induced sister chromatid exchange and chromosomal aberrations. It did not induce unscheduled DNA synthesis in rat cells exposed either *in vitro* or *in vivo*. *In vivo* in rats, it bound to macromolecules, but not to DNA. It did not induce micronuclei in mouse bone marrow *in vivo*.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of nitrotoluenes.

There is *limited evidence* in experimental animals for the carcinogenicity of 2-nitrotoluene.

There is *inadequate evidence* in experimental animals for the carcinogenicity of 3- and 4-nitrotoluenes.

Overall evaluation

Nitrotoluenes are *not classifiable as to their carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonyms for 2-nitrotoluene

- 2-Methylnitrobenzene
- *ortho*-Methylnitrobenzene
- 2-Methyl-1-nitrobenzene
- *ortho*-Mononitrotoluene
- 2-Nitrotoluol
- *ortho*-Nitrotoluol

Synonyms for 3-nitrotoluene

- 3-Methylnitrobenzene
- *meta*-Methylnitrobenzene
- 3-Methyl-1-nitrobenzene
- *meta*-Mononitrotoluene
- 3-Nitrotoluol
- *meta*-Nitrotoluol

Synonyms for 4-nitrotoluene

- 4-Methylnitrobenzene

- *para*-Methylnitrobenzene
- 4-Methyl-1-nitrobenzene
- *para*-Nitrotoluene
- 4-Nitrotoluol
- *para*-Nitrotoluol

Last updated 08/14/1997

TETRANITROMETHANE

(Group 2B)

For definition of Groups, see [Preamble Evaluation](#).

Vol.: 65 (1996) (p. 437)

CAS No.: 509-14-8

Chem. Abstr. Name: Tetranitromethane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Tetranitromethane is produced commercially by nitration of acetic anhydride or acetylene. Tetranitromethane has been used as an oxidizer in rocket propellants and explosives. Few data are available on human exposure to tetranitromethane.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Tetranitromethane was tested for carcinogenicity in one study in mice and in one study in rats by inhalation exposure. The incidence of alveolar-bronchiolar adenomas and carcinomas was markedly increased in treated mice and rats, and the incidence of squamous-cell carcinomas of the lung was increased in treated rats.

5.4 Other relevant data

No human or experimental animal data were available to the Working Group on the absorption, distribution, metabolism or excretion of tetranitromethane.

No human data were available on the toxic effects of tetranitromethane.

Tetranitromethane induced lethargy, reduced body-weight gain and inflammatory changes in the upper and lower respiratory tract of rats and mice.

Tetranitromethane is genotoxic in bacteria and cultured mammalian cells. Tumours from tetranitromethane-treated rats and mice had a GC:AT transition in the second base of codon 12 of the K-*ras* oncogene.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of tetranitromethane.

There is *sufficient evidence* in experimental animals for the carcinogenicity of tetranitromethane.

Overall evaluation

Tetranitromethane is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonyms

- Tetan
- TNM

Last updated 08/14/1997

2,4,6-TRINITROTOLUENE

(Group 3)

For definition of Groups, see [Preamble Evaluation](#).

Vol.: 65 (1996) (p. 449)

CAS No.: 118-96-7

Chem. Abstr. Name: 2-Methyl-1,3,5-trinitrobenzene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

2,4,6-Trinitrotoluene is produced commercially by the nitration of toluene. It is used mainly as a high explosive in military and industrial applications. Exposures to 2,4,6-trinitrotoluene both through inhalation and skin absorption can occur during its production, during munitions manufacturing and loading, and during blasting operations. 2,4,6-Trinitrotoluene has been detected in wastewater, surface and groundwater, and in soils and sediments near plants manufacturing 2,4,6-trinitrotoluene and explosives.

5.2 Human carcinogenicity data

One ecological study was available that noted an association between leukaemia and residence in an area contaminated with 2,4,6-trinitrotoluene.

5.3 Animal carcinogenicity data

No adequate study on the carcinogenicity of 2,4,6-trinitrotoluene in experimental animals was available to the Working Group.

5.4 Other relevant data

In humans, absorption of 2,4,6-trinitrotoluene both through the skin and the gastrointestinal route had been demonstrated. 2,4,6-Trinitrotoluene is also probably absorbed in the respiratory tract. However, the dermal route is the commonest in occupational settings.

In humans exposed to 2,4,6-trinitrotoluene, mainly dinitroaminotoluenes and also diaminonitrotoluenes, probably mainly as conjugates, as well as unchanged 2,4,6-trinitrotoluene were found in the urine.

In humans, exposure to 2,4,6-trinitrotoluene has been found to cause haematological disorders, including aplastic anaemia, haematolytic anaemia and methaemoglobinaemia. 2,4,6-Trinitrotoluene may cause toxic hepatitis. Moreover, allergic contact dermatitis and cataract may occur, as well as gastritis and respiratory mucous membrane and conjunctival irritation.

2,4,6-Trinitrotoluene undergoes both oxidative and reductive metabolism in animals. It causes anaemia and hepatotoxicity in rats and dogs. Testicular atrophy occurs in rats following exposure to 2,4,6-trinitrotoluene.

In workers exposed to 2,4,6-trinitrotoluene, increased bacterial mutagenic activity was found in the urine.

2,4,6-Trinitrotoluene is mutagenic in bacteria with and without a metabolic activation system. In cultured mammalian cells, it is mutagenic only in the absence of a metabolic activation system. Although 2,4,6-

trinitrotoluene was negative in mammals *in vivo* for unscheduled DNA synthesis in the liver and micronuclei induction in bone marrow, the urine of rats is mutagenic after intraperitoneal injection of 2,4,6-trinitrotoluene.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 2,4,6-trinitrotoluene.

There is *inadequate evidence* in experimental animals for the carcinogenicity of 2,4,6-trinitrotoluene.

Overall evaluation

2,4,6-Trinitrotoluene is *not classifiable as to its carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonyms

- Entsufon
- Gradetol
- Methyltrinitrobenzene
- 1-Methyl-2,4,6-trinitrobenzene
- Nitropel
- TNT
- α -TNT
- Tolit
- Tolite
- Trilit
- Trinitrotoluene
- α -Trinitrotoluol
- s-Trinitrotoluene
- s-Trinitrotoluol
- *sym*-Trinitrotoluene
- *sym*-Trinitrotoluol
- Tritol
- Trotyl
- Trotyl oil

MUSK AMBRETTE AND MUSK XYLENE (Group 3)

For definition of Groups, see [Preamble Evaluation](#).

Vol.: 65 (1996) (p. 477)

CAS No.: 83-66-9

Chem. Abstr. Name: 1-(1,1-Dimethylethyl)-2-methoxy-4-methyl-3,5-dinitrobenzene

CAS No.: 81-15-2

Chem. Abstr. Name: 1-(1,1-Dimethylethyl)-3,5-dimethyl-2,4,6-trinitrobenzene

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Musk ambrette and musk xylene are nitro musks, which are prepared by nitration of *tert*-butylcresol methyl ether and *tert*-butyl-*meta*-xylene, respectively. Musk xylene and, in lower amounts, musk ambrette have been used since the early 1900s as fragrance ingredients in perfumes, soaps, detergents and cosmetics. Musk ambrette has also been used at low levels in foods such as candy, chewing gum and beverages. Nitro musks have been detected in surface waters and in fish and shellfish.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

No data were available on the carcinogenicity of musk ambrette.

Musk xylene was tested for carcinogenicity in mice by oral administration in the diet in one experiment and induced increased incidences of hepatocellular adenomas and carcinomas and Harderian gland tumours in males and hepatocellular adenomas in females.

5.4 Other relevant data

Application of musk ambrette on the skin may cause photocontact dermatitis and chronic actinic dermatitis.

Musk ambrette was mutagenic in *Salmonella* and *Drosophila*. It did not induce micronuclei in the bone marrow of mice *in vivo*.

In humans, musk xylene is absorbed from the gastrointestinal tract. It is distributed to the adipose tissue and its half-time in blood plasma is two to three months. It is excreted in human milk.

Musk xylene is metabolized in the rat by nitroreduction. Musk xylene is a phenobarbital-type inducer of cytochromes P450 in rats and mice.

Musk xylene did not induce genetic damage in bacteria, cultured mammalian cells or, in one study, in mammals *in vivo*.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of musk ambrette and musk xylene.

There is *inadequate evidence* in experimental animals for the carcinogenicity of musk ambrette.

There is *limited evidence* in experimental animals for the carcinogenicity of musk xylene.

Overall evaluation

Musk ambrette and musk xylene are *not classifiable as to their carcinogenicity to humans (Group 3)*.

For definition of the italicized terms, see [Preamble Evaluation](#).

Synonyms for musk ambrette

- Amber musk
- Artificial musk ambrette
- 5-*tert*-Butyl-1,3-dinitro-4-methoxy-2-methylbenzene
- 4-*tert*-Butyl-3-methoxy-2,6-dinitrotoluene
- 2,6-Dinitro-3-methoxy-4-*tert*-butyltoluene
- Synthetic musk ambrette

Synonyms for musk xylene

- 1-*tert*-Butyl-3,5-dimethyl-2,4,6-trinitrobenzene
- Musk xylol
- 2,4,6-Trinitro-1,3-dimethyl-5-*tert*-butylbenzene
- 2,4,6-Trinitro-3,5-dimethyl-*tert*-butylbenzene
- Xylene musk