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A REVIEW OF HUMAN CARCINOGENS

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IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

MOPP

MOPP was considered by a previous IARC Working Group in 1987 (IARC, 1987a). Since that time, new data have become available, these have been incorporated into the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

1.1.1 MOPP

MOPP is a combination chemotherapy regimen, the acronym being derived from the first initials of its constituents (as they were referred to at the time it was developed, i.e. mechlorethamine, oncovin, procarbazine, and prednisone).
Chem. Abstr. Serv. Reg. No.: 113803-47-7
Chem. Abstr. Name: Vincaleukoblastine, 22-oxo-, mixture with 2-chloro-*N*-(2-chloroethyl)-*N*-methylethanamine hydrochloride, 17,21-dihydroxypregna-1,4-diene-3,11,20-trione and *N*-(1-methylethyl)-4-[(2-methylhydrazino)methyl]benzamide
Synonyms: Vincristine-prednisone-nitrogen mustard-procarbazine mixture

1.1.2 Chlormethine

Chem. Abstr. Serv. Reg. No.: 51-75-2; 55-86-7 [hydrochloride]
Chem. Abstr. Name: Ethanamine, 2-chloro-*N*-(2-chloroethyl)-*N*-methyl-
IUPAC Systematic Name: 2-Chloro-*N*-(2-chloroethyl)-*N*-methylethanamine

Synonyms: Bis(β-chloroethyl)methylamine; bis(2-chloroethyl)methylamine; *N,N*-bis(2-chloroethyl)methylamine; Caryolysine; chloramine; chlorethazine; di(2-chloro-ethyl)methylamine; *N,N*-di(chloroethyl)methylamine; mechlorethamine; methyl-β,β-dichlorodiethylamine; methylbis(β-chloroethyl)amine; methylbis(2-chloroethyl)amine; methyldi(2-chloroethyl)amine; *N*-methyl-2,2'-dichlorodiethylamine; *N*-methylbis(β-chloroethyl)amine; *N*-methylbis(2-chloroethyl)amine; Mustargen; nitrogen mustard
Description: hygroscopic, light yellow brown crystalline powder [hydrochloride salt] (McEvoy, 2007); also reported as white or almost white crystalline powder [hydro-chloride salt] (Sweetman, 2008)

(a) *Structural and molecular formulae, and relative molecular mass*
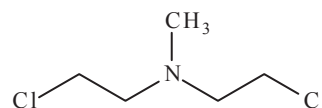
$C_5H_{11}Cl_2N$
Relative molecular mass: 156.1

1.1.3 Vincristine

Chem. Abstr. Serv. Reg. No.: 57-22-7; 2068-78-2 [sulfate salt]
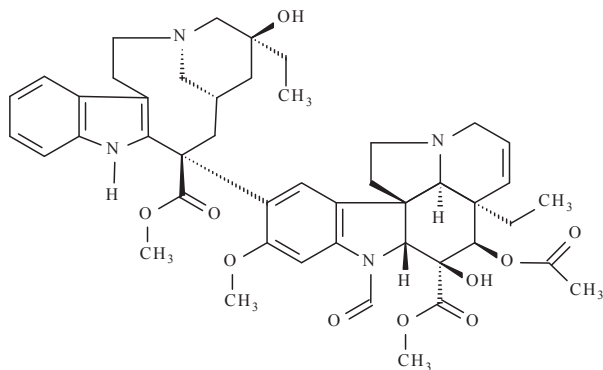*Chem. Abstr. Name*: Vincaleukoblastine, 22-oxo
IUPAC Systematic Name: Leurocristine
Synonyms: LCR; leucristine; Oncovin; VCR; Vincasar PFS; (+)-vincristine
Description: white, off-white, or slightly yellow, hygroscopic, amorphous or crystalline powder [sulfate salt] (McEvoy, 2007; Sweetman, 2008)

(a) *Structural and molecular formulae, and relative molecular mass*

$C_{46}H_{56}N_4O_{10}$
Relative molecular mass: 825.0

1.1.4 Procarbazine

Chem. Abstr. Serv. Reg. No.: 671-16-9; 366-70-1 [hydrochloride]
Chem. Abstr. Name: Benzamide, *N*-(1-methylethyl)-4-[(2-methylhydrazino) methyl]-
IUPAC Systematic Name: 4-[(2-Methylhydrazinyl) methyl]-*N*-propan-2-ylbenzamide
*Synonyms*: Benzamide, *N*-(1-methylethyl)-4-[(2-methylhydrazino)methyl]-; 1-methyl-2-[*p*-(isopropylcarbamoyl) benzyl]hydrazine; 4-[(2-methylhy-drazino)methyl]-*N*-isopropylbenzamide;

p-(2-methylhydrazinomethyl)-*N*-isopropylbenzamide; *N*-isopropyl-*α*-(2-methylhydrazino)-*p*-toluamide.
Description: white to pale yellow, crystalline powder with a slight odour [hydrochloride salt] (McEvoy, 2007)

(a) *Structural and molecular formulae, and relative molecular mass*
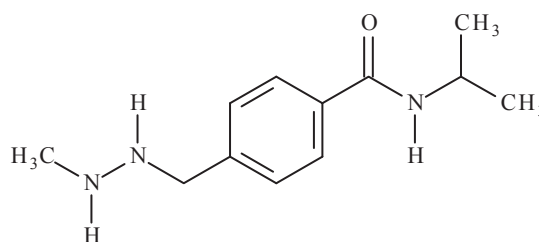
$C_{12}H_{19}N_3O$
Relative molecular mass: 221.3

1.1.5 Prednisone

Chem. Abstr. Serv. Reg. No.: 53-03-2
Chem. Abstr. Name: Pregna-1,4-diene-3,11,20-trione, 17,21-dihydroxy-
IUPAC Systematic Name: (8S,9S,10R,13S,14S,17R)-17-Hydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-6,7,8,9,12,14,15,16-octahydrocyclopenta[*a*] phenanthrene-3,11-dione
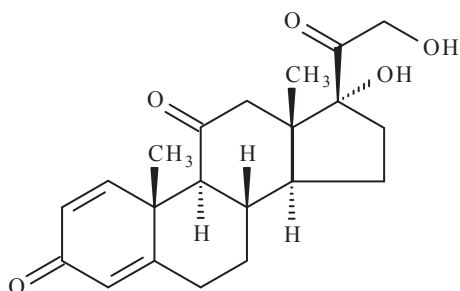*Synonyms*: 1,2-Dehydrocortisone; 17,21-dihydroxypregna-1,4-diene-3,11,20-trione; 17*α*,21-dihydroxy-1,4-pregnadiene-3,11,20-trione
Description: white to practically white, odourless, crystalline powder (McEvoy, 2007; Sweetman, 2008)

(a) *Structural and molecular formulae, and relative molecular mass*

$C_{21}H_{26}O_5$

Relative molecular mass: 358.4

1.2 Use of the combination

Information for Section 1.2 is taken from Fischer et al. (2003), McEvoy (2007), Skeel (2007), and Sweetman (2008).

1.2.1 Indications

MOPP, developed in the mid-1960s, was the first combination chemotherapy regimen for treating Hodgkin lymphoma. It has been used alone or in combination (in part or total) with ABVD [adriamycin, bleomycin, vinblastine, dacarbazine] chemotherapy.

1.2.2 Dosage

In the treatment of advanced Hodgkin lymphoma, the usual dose of chlormethine hydrochloride in the MOPP regimen is 6 mg/m² given intravenously on Days 1 and 8 of a 28-day cycle. In subsequent cycles of MOPP therapy, dose reductions are sometimes considered depending on the depth and duration of treatment-induced neutropenia or thrombocytopenia.

The usual recommended adult dose of vincristine sulfate is 1.4 mg/m² on Days 1 and 8 of a 28-day cycle, often limiting the dose to 2 mg in adults, and the usual paediatric dose is 1.5–2 mg/m². For children weighing 10 kg or less, the recommended therapy is initiated at 0.05 mg/kg once weekly. The dose of procarbazine is 100 mg/m² daily on Days 1 to 14 of a 28-day cycle. The dose of prednisone is 40 mg/m² daily on Days 1 to 14, on Cycles 1 and 4 only. The MOPP regimen is repeated every 28 days for a total of 4–8 courses depending on the response to treatment, and on the initial stage of Hodgkin lymphoma.

Chlormethine (as the hydrochloride) is available as a 10 mg injection solution for intravenous administration. Vincristine (as the sulfate) is available as a 1 mg/mL (1 and 2 mg) injection solution for intravenous-only administration. Procarbazine (as the hydrochloride) is available as a 50 mg (procarbazine equivalent) capsule for oral administration. Prednisone is available as 1, 2.5, 5, 10, 20, and 50 mg tablets for oral administration, and as 5 mg/5 mL or 5 mg/mL solutions for oral administration.

1.2.3 Trends in use

ABVD has supplanted MOPP as the regimen of choice for the initial treatment of Hodgkin lymphoma. MOPP is sometimes used if patients fail to respond or relapse after ABVD treatment, although other regimens have been developed that are used when autologous stem-cell transplantation is considered as salvage therapy.

2. Cancer in Humans

2.1 Acute myeloid leukaemia

MOPP was one of the first attempts at combining several active agents in the treatment of cancer and, until about 15 years ago, was the most common regimen used for the treatment of Hodgkin lymphoma (Devita *et al.*, 1970). In 1972, roughly 5 years after the introduction of intensive combined chemotherapy for Hodgkin disease, the first report of subsequent acute

myeloid leukaemia appeared (Arseneau *et al.*, 1972). Since then, multiple centres and collaborative treatment groups in Europe and North America have performed studies that led to the conclusion that MOPP treatment was causally associated with subsequent acute myeloid leukaemia, and myelodysplastic syndromes (Baccarani *et al.*, 1980; Brusamolino *et al.*, 1982; Coltman & Dixon, 1982; Glicksman *et al.*, 1982; Boivin *et al.*, 1984; IARC, 1987a). Summary estimates of the relative risk of acute myeloid leukaemia after MOPP chemotherapy relative to a healthy population have been calculated to vary from 9 (Jacquillat *et al.*, 1983) through 40 (Bergsagel *et al.*, 1982; Henry-Amar, 1983) to well over 100 (Glicksman *et al.*, 1982; Bartolucci *et al.*, 1983; Boivin *et al.*, 1984). The rates of acute myeloid leukaemia/myelodysplastic syndromes were highest in patients receiving combined modality therapy in which MOPP was combined with irradiation.

[The Working Group noted that observed variations in both relative and actuarial risks are probably due to differences in methodology, treatment, and patient populations. Furthermore, although cases of acute myeloid leukaemia can occur at any time after initial treatment, there is a sharp peak in incidence approximately 4–7 years after treatment with alkylating-agent-based chemotherapy with much lower rates both before and afterwards (Blayney *et al.*, 1987).]

[The Working Group noted that the use of multi-agent chemotherapy regimens makes the identification of risk from individual constituents very difficult, although the focus in the MOPP regimen has been on the nitrogen mustard (Henry-Amar *et al.*, 1989) and procarbazine because there is little evidence of leukaemogenesis from vinca alkaloids or corticosteroids.]

Randomized trials have shown that ABVD produced a lower incidence of acute myeloid leukaemia in ABVD recipients than in MOPP recipients (Santoro *et al.*, 1987; Cimino *et al.*, 1991; Maurizi Enrici *et al.*, 1997; Cellai *et al.*,

2001; Duggan *et al.*, 2003) thereby providing further indirect evidence that MOPP is involved in the higher rates of acute myeloid leukaemia observed in the earlier studies, rather than the underlying Hodgkin lymphoma.

2.2 Cancer of the lung

A nested case–control study of 222 cases of lung cancer occurring among 19046 patients treated for Hodgkin lymphoma resulted in a relative risk of 4.2 (95%CI: 2.1–8.8; adjusted for smoking history) for patients treated with alkylating agents in general, and 5.0 (95%CI: 2.1–13.6) for those treated with MOPP specifically, with increasing risks with higher cumulative doses of both chlormethine and procarbazine (Travis *et al.*, 2002). Two smaller case–control studies of lung cancer in patients with Hodgkin lymphoma concurred with this evidence (Kaldor *et al.*, 1992; Swerdlow *et al.*, 2001).

See Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100A/100A-07-Table2.1.pdf

2.3 Other sites

As noted in the earlier *IARC Monograph* (IARC, 1987a) and supported by more recent publications, the development of other tumours, including non-Hodgkin lymphoma, breast cancer (Kaldor *et al.*, 1987), sarcoma, melanoma (Tucker *et al.*, 1985), malignancies of the central nervous system, and carcinomas of the thyroid and gastrointestinal system have also been reported to increase after treatment for Hodgkin lymphoma (Boivin *et al.*, 1984; Cellai *et al.*, 2001). [The Working Group noted that estimates in these studies were generally based on few outcomes, and are difficult to interpret. In addition, soft tissue sarcomas, as well as cancers of the lung, breast, and thyroid occur predominantly in areas of prior irradiation, thus

making it even more complicated to estimate the contribution of MOPP in the development of these cancers, which can develop decades after successful completion of therapy for Hodgkin lymphoma.]

3. Cancer in Experimental Animals

No data were available to the Working Group.

4. Other Relevant Data

Each of the drugs used in the MOPP combined chemotherapy has a unique or complementary mechanism of action, and has been previously evaluated by IARC (IARC, 1987b).

Chlormethine was considered by IARC Working Groups in 1975 and 1987 (IARC, 1975, 1987b).

In humans, following its in-vivo administration, chlormethine is rapidly converted into an ethylene immonium ion which reacts with the guanine residues in adjacent strands of DNA as well as with thiol groups of proteins (Boyland, 1946; Verly, 1964). It is usually cleared from the blood in a few minutes. A very small proportion is excreted unchanged in the urine (Sweetman, 2008). An intravenous administration of chlormethine to dogs cleared rapidly from the blood, with 0.01% found in the urine, low levels found in the tissues, the highest concentration being in the bone marrow (Ishidate, 1959; Mellett & Woods, 1960). After intravenous injection of $^{14}CH_3$-chlormethine to mice, significant levels of the radioactivity were observed in the brain, spinal cord, lungs, and submaxillary glands (Tubaro & Bulgini, 1968). In rats, 16% of an injected dose of chlormethine was found present in the spleen, lung, kidney, liver and blood, and 17% was excreted in the urine (Obrecht et al., 1964).

Chlormethine is a bifunctional alkylating agent that binds to DNA, forming mono-adducts primarily at the N^7 position of guanine, and interstrand and intrastrand cross-links (Povirk & Shuker, 1994). As indicated in earlier *IARC Monographs* (IARC, 1987b), chlormethine induced dominant lethal mutations and micronuclei in the bone-marrow cells of mice exposed *in vivo,* and alkylated DNA of ascites cells in experimental animals treated *in vivo*. It induced chromosomal aberrations, sister chromatid exchange, and unscheduled DNA synthesis in human cells *in vitro*. In rodent cells *in vitro*, it induced sister chromatid exchange, chromosomal aberrations and DNA damage; studies on the induction of mutation were inconclusive. It transformed mouse C3H 10T1/2 cells. Chlormethine induced aneuploidy and somatic mutation and recombination in *Drosophila*, chromosomal aberrations in plants, mitotic recombination and mutation in fungi, and mutation and DNA damage in fungi. It was also reported in one study to induce chromosomal aberrations in lymphocytes of treated patients.

Vincristine sulfate was considered by IARC Working Groups in 1981 and 1987 (IARC, 1981, 1987b).

After intravenous injection in humans, vincristine is extensively protein-bound and is reported to be concentrated in blood platelets. It is cleared rapidly from the blood, metabolized in the liver, and excreted primarily in the bile, about 70–80% of a dose is found in faeces, as unchanged drug and metabolites, while 10–20% appears in the urine over a 72-hour period (Bender et al., 1977; Jackson et al., 1978). The terminal half-life may range from 19–155 hours. Vincristine does not appear to cross the blood–brain barrier (Sweetman, 2008).

After intravenous or intraperitoneal injection of vincristine to different animal species, it is cleared from the blood and distributed to most tissues (lung, liver, kidney, pancreas, spleen, and brain) (Castle et al., 1976; El Dareer et al., 1977a;

Jackson *et al.*, 1980). It is excreted in urine and faeces as unchanged drug and as metabolites in approximately the same proportions. In mice and monkeys, a very low concentration of vincristine appears to cross the blood–brain barrier (El Dareer *et al.*, 1977a; Jackson *et al.*, 1980).

Vincristine sulfate is a Vinca alkaloid that interferes with microtubule assembly and spindle formation and consequently blocks the replication of cells during mitosis. As indicated in earlier *IARC Monographs* (IARC, 1987b), it induced micronuclei in the bone-marrow cells of mice and hamsters treated *in vivo*. It induced aneuploidy in and transformation of Syrian hamster embryo cells, but did not transform mouse C3H 10T1/2 cells. It did not induce structural chromosomal aberrations, sister chromatid exchange or unscheduled DNA synthesis in rodent cells *in vitro*. It induced mutation in mouse lymphoma cells but not in other rodent cells. It did not induce sex-linked recessive lethal mutations in *Drosophila*, and was not mutagenic to bacteria.

Procarbazine (hydrochloride) was considered by IARC Working Groups in 1981 and 1987 (IARC, 1981, 1987b).

In humans, procarbazine is given orally as it is absorbed readily from the gastrointestinal tract. The plasma half-life is approximately 7 minutes (Raaflaub & Schwartz, 1965). It is rapidly metabolized to azo derivatives and hydrogen peroxide (mainly in the liver and the kidneys), and only about 5% is excreted unchanged in the urine (Oliverio, 1973). Using ^{14}C-radiolabelled procarbazine, 70% was shown to appear in urine within 24 hours, less than 5% as the unchanged parent compound, and the remainder predominantly as *N*-isopropylterephthalamic acid. Between 10–20% of the drug is exhaled as carbon dioxide and methane via the lungs. Faecal excretion is negligible (Bollag, 1965; Schwartz *et al.*, 1967). After intravenous injection in humans and in dogs, the drug and its metabolites cross the blood–brain barrier, and diffuses in the cerebrospinal fluid within a short time, which may account for some of its central nervous toxicity (Oliverio, 1973).

In animals, after oral administration, procarbazine is also readily absorbed from the gut. Its plasma half-life in dogs and rats is 12 and 24 minutes, respectively (Raaflaub & Schwartz, 1965; Reed, 1975). In rodents and dogs, the main urinary metabolite is *N*-isopropylterephthalamic acid (Oliverio *et al.*, 1964). Methane and carbon dioxide can be exhaled after intraperitoneal injection to rats suggesting that the metabolism of procarbazine proceeds via formation of methylhydrazine (Dost & Reed, 1967). Procarbazine and its metabolite monomethylhydrazine are demethylated by rat hepatic enzymes, forming the azo and azoxy metabolites (Baggiolini & Bickel, 1966). In rats, *N*-isopropyl-*para*-toluamide and methane were also found as metabolites (Weinkam & Shiba, 1978).

Procarbazine is a methylhydrazine derivative metabolized to reactive intermediates that decompose to produce a methyl diazonium cation, which methylates DNA, and is believed to be responsible for its toxic and carcinogenic effects (Kufe *et al.*, 2006). As summarized in earlier *IARC Monographs* (IARC, 1987b), procarbazine gave positive results for germ-cell mutation in the mouse-specific locus test, and caused mutation in the mouse spot test. It induced micronuclei and structural chromosomal aberrations in mice treated *in vivo*, but conflicting results were obtained in tests for dominant lethal mutations and negative results in the heritable translocation test. It induced sister chromatid exchange in mice and Chinese hamsters, and caused DNA damage in rodents treated *in vivo*. Procarbazine did not transform Syrian hamster embryo cells. It induced mutation but not sister chromatid exchange in rodent cells *in vitro*. It induced aneuploidy, dominant lethal mutations, sex-linked recessive lethal mutations and somatic mutation and recombination in *Drosophila*, but did not cause heritable translocations. It induced

mutation, gene conversion and mitotic recombination in fungi. Conflicting results were obtained for mutation in bacteria, both *in vitro* and in host-mediated assays; it induced DNA damage in bacteria.

Prednisone was considered by IARC Working Groups in 1981 and 1987 (IARC, 1981, 1987b).

Prednisone is readily absorbed from the gastrointestinal tract in animals and humans. Prednisone and prednisolone, its active metabolite, have been detected in serum within 1 hour after prednisone administration by different routes in different species (Colburn *et al.*, 1976; El Dareer *et al.*, 1977b).

Prednisone is converted to prednisolone, its biologically active form, after the reduction of the 11-oxo to the 11-β-hydroxyl group catalysed by the enzyme 11-β-hydroxydehydrogenase (Jenkins & Sampson, 1967), and to several other metabolites (El Dareer *et al.*, 1975, 1977b). Metabolism takes place primarily in the liver. After intravenous administration of prednisone to a monkey, the unchanged drug and prednisolone were distributed to most of the tissues with the highest concentrations in the kidneys for prednisone, and in the liver for prednisolone (El Dareer *et al.*, 1977b).

In humans, orally administered prednisone produces lower circulating concentrations of prednisolone than prednisolone itself given by the same route (Tse & Welling, 1979), with considerable intra- and intersubject variation (Hsueh *et al.*, 1979).

Prednisone is bound to serum proteins (albumin and corticosteroid-binding globulin) in humans and animals (Lang & Stevens, 1970; Feldman *et al.*, 1972; Pickup, 1979).

In humans, prednisone is excreted in urine with a greater level after intravenous administration than after oral dosage (Hsueh *et al.*, 1979). The corresponding 20 β-alcohols such as 20-dihydroprednisolone are present in smaller amounts (Gray *et al.*, 1956). Other uncommon metabolites are mentioned in Bush & Mahesh (1964).

Prednisone is a synthetic glucocorticoid with multiple modes of action, and produces a range of anti-inflammatory and immunosuppressive effects (Sweetman, 2008). In the earlier *IARC Monographs* (IARC, 1987b), it was reported that there were no data available on the genetic and related effects of prednisone in humans. It was also indicated that prednisone did not induce chromosomal aberrations in bone-marrow cells of rats treated *in vivo*, and was not mutagenic to bacteria.

In addition to studies on the individual drugs, there have been several investigations into the genotoxic effects of this drug combination. For example, Clare *et al.* (1982) investigated the ability of the MOPP drug combination to induce sister chromatid exchange in peripheral blood lymphocytes exposed in culture, and determined that the resulting dose-related increase in sister chromatid exchange was very similar to that seen with chlormethine alone. In another series of studies, Goldstein (1984, 1987, 1987–1988) tested MOPP as well as three of its components (chlormethine, vincristine, and procarbazine) individually and in combination for their ability to induce dominant lethal mutations using an in-vitro assay following the in-vivo treatment of mice. Significant increases were reported for MOPP, chlormethine, and procarbazine (Goldstein, 1984; 1987–1988). In a follow-up study, significant increases in mutation were seen with chlormethine alone and in the two- and three-drug combinations that contained chlormethine, leading to the conclusion that the observed increases were primarily due to chlormethine (Goldstein, 1987). Similarly, the mutagenic and genotoxic effects of the drug combination have been investigated in cancer patients undergoing treatment (Sen *et al.*, 1990; Caggana *et al.*, 1991; Brandriff *et al.*, 1994; Abdallah *et al.*, 1995; Zheng *et al.*, 2000; Bilban-Jakopin & Bilban, 2001; Mkacher *et al.*, 2003). In

most of the reports, the patients were also being treated with ionizing radiation or other antineoplastic drugs so that when effects were seen, it was not possible to determine which effects or portion of the effects were due to the MOPP treatment. However, in many of these reports, there were individuals or groups of patients who had only received MOPP and who showed elevated frequencies of mutation, sister chromatid exchange or chromosomal aberrations in their peripheral blood lymphocytes or sperm (Brown et al., 1988; Sen et al., 1990; Caggana et al., 1991; Brandriff et al., 1994; Zheng et al., 2000). While considerable variability in response was seen, these reports are largely consistent with the in-vitro and animal results, indicating that the drug combination is mutagenic and genotoxic. Myelotoxicity is also commonly seen in patients treated with this combination of drugs (Benjamin et al., 1976).

Acute myeloid leukaemia that develops in patients that have previously been treated with alkylating agents such as chlormethine and procarbazine frequently exhibits distinctive characteristics that allow it to be distinguished from acute myeloid leukaemia induced by other agents (such as topoisomerase II inhibitors) or acute myeloid leukaemia that occurs spontaneously (Pedersen-Bjergaard & Rowley, 1994; Jaffe et al., 2001; Mauritzson et al., 2002; Pedersen-Bjergaard et al., 2006). One of the hallmarks of leukaemias induced by alkylating agents is that they frequently exhibit a clonal loss of either chromosome 5 or 7 (−5, −7) or a loss of part of the long arm of one of these chromosomes (5q−, 7q−). For example, a deletion within the long arm of chromosome 5 involving the bands q23 to q32 is often seen (Jaffe et al., 2001). Leukaemias that have developed in patients treated with MOPP (often in combination with other agents) have been reported to exhibit these clonal chromosomal changes (Christiansen et al., 2001; Hayani et al., 1992).

In addition, mutations in *TP53* are frequently seen in leukaemias with the −5/5q− karyotype, and mutations involving the *AML1* gene as well as mutations in *TP53* and *RAS* are often seen in a subset of leukaemias that exhibit the −7/7q− karyotype (Christiansen et al., 2001, 2005; Pedersen-Bjergaard et al., 2006). These treatment-related acute myeloid leukaemias also frequently exhibit increased methylation of the *p15* promoter (Pedersen-Bjergaard et al., 2006). Although the evidence that MOPP directly induces losses or deletions affecting chromosomes 5 or 7 is limited, the individual drugs have been reported to induce similar types of chromosomal alterations in a variety of experimental models as described above.

4.1 Synthesis

The MOPP combination as well as individual components, except for prednisone, are genotoxic, and induce cancer via a genotoxic mechanism.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of MOPP. MOPP causes cancer of the lung, and acute myeloid leukaemia.

No data were available to the Working Group for the carcinogenicity of MOPP in experimental animals.

MOPP is *carcinogenic to humans (Group 1)*.

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