This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 14-21 October 2008.

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS
TREOSULFAN

Treosulfan was considered by previous IARC Working Groups in 1980 and 1987 (IARC, 1981, 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

Chem. Abstr. Name: 1,2,3,4-Butanetetrol, 1,4-dimethanesulfonate, (2S, 3S)-
IUPAC Systematic Name: [(2S,3S)-2,3-Dihydroxy-4-methylsulfonyloxybutyl]methane-
sulfonate
Synonyms: 1,2,3,4-Butanetetrol, 1,4-di-
methanesulfonate, [S-(R*,R*)]-; dihydroxy-
busulfan; dihydroxymyleran; Ovastat;
(2S,3S)-threitol 1,4-bismethanesulfonate;
L-threitol 1,4-bis(methanesulfonate)
Description: White, odourless, crystalline powder (IARC, 1981)

1.1.1 Structural and molecular formulae, and relative molecular mass

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\begin{align*}
\text{C}_6\text{H}_{14}\text{O}_8\text{S}_2 \\
\text{Relative molecular mass: 278.3}
\end{align*}
\]

1.2 Use of the agent

Treosulfan is a prodrug of a bifunctional alkylating cytotoxic agent (Scheulen et al., 2000; Sweetman, 2008).

1.2.1 Indications

Treosulfan is used to treat ovarian cancer (Royal Pharmaceutical Society of Great Britain, 2007). In addition, preclinical and clinical activity have been demonstrated against some other solid tumours, and haematological malignancies (Scheulen et al., 2000). It has also been used for bone-marrow ablation before stem-cell transplantation, and to treat malignant melanoma, and breast cancer.

1.2.2 Dosage

Treosulfan is given orally or by intravenous or intraperitoneal administration. Treosulfan is available as 1 g and 5 g powders for reconstitution for injection or as a 250 mg capsule (Royal Pharmaceutical Society of Great Britain, 2007).
1.2.3 Trends in use

Treosulfan is commercially available in Europe for the treatment of ovarian cancer. In the USA, treosulfan is under clinical development and, at the time of writing, had not yet received approval from the US Food and Drug Administration (FDA) (Anakena, 2008). In April 2011, the US National Cancer Institute Clinical Trials database listed 15 active clinical trials using treosulfan, alone or in combination, in the treatment regimens (NCI, 2011). Treosulfan is listed in the FDA’s orphan drug database (FDA, 2008).

2. Cancer in Humans

The first evaluation of treosulfan as a carcinogen (IARC, 1981) was based on the earlier results of the Danish cohort described below.

Two epidemiological studies have focused on the risk of leukaemia following treatment with treosulfan. In a cohort of 553 Danish patients with ovarian cancer treated only with treosulfan and followed for 9 years (over 1700 person–years) after treatment, 13 patients developed acute myeloid leukaemia, mostly within 5 years after the start of chemotherapy. The relative risk of acute myeloid leukaemia was in excess of 100, and there was a significant correlation between cumulative dose of treosulfan and risk of leukaemia (Pedersen-Bjergaard et al., 1985). In an international case–control study of women treated for ovarian cancer, Kaldor et al. (1990) found that the relative risk was 3.6 in the group treated with the lowest dose of treosulfan, and 33.0 within the highest dose group. [The Working Group noted that there may have been an overlap between the two studies, as the case–control study included Denmark, and covered a similar time period as the Danish cohort study.]

3. Cancer in Experimental Animals

No data were available to the Working Group.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

Treosulfan is a prodrug that is converted non-enzymatically first to a mono-epoxide – (2S,3S)-1,2-epoxy-3,4-butanediol-4-methanesulfonate – and then to a diepoxide – L-diepoxybutane, which is also a metabolite of butadiene – under physiological conditions. Such conversions are assumed to account for the alkylating and therapeutic activities of treosulfan. After oral and intravenous administration of treosulfan to humans, the parent drug is found in the serum at a higher concentration after the intravenous dosing, and about 15% of unchanged drug is excreted in urine (Hilger et al., 2000).

4.2 Genotoxic effects

4.2.1 Interaction with DNA

As a bifunctional alkylating agent, treosulfan alkylates DNA and creates interstrand cross-links in cell-free systems (plasmid DNA), and in intact cells (Hartley et al., 1999), preferentially at guanine residues. Prior to any short-term tests for genotoxicity, treosulfan was predicted to be active based on its structure (Shelby, 1988).

4.2.2 Mutagenicity in vitro

Treosulfan is mutagenic in Salmonella typhimurium strains TA100 and TA1535 in the absence of metabolic activation, as is diepoxybutane without external activation (Zeiger & Pagano, 1989). These strains detect base-pair substitutions at G:C base pairs. Treosulfan is
not mutagenic to TA102, which is sensitive to base-pair substitutions at A:T (Abu-Shakra et al., 2000).

Treosulfan is mutagenic in Chinese hamster ovary cells, at the guanine phosphorybosyl transferase (Gpt) locus (Zhu & Zeiger, 1993); diepoxybutane is also mutagenic, but at a lower concentration.

4.2.3 Mutagenicity in vivo

Earlier literature contains reports that treosulfan induced chromosomal aberrations in several plant species, including Allium cepa (onion), Hordeum sativum (barley), Nigella damascena (love-in-a-mist), and Vicia faba (vetch), but did not produce chlorophyll mutations in Arabidopsis thaliana (thale cress) (IARC, 1981, 1987b). Subsequently, in an in-vivo study, treosulfan gave positive results in a mouse bone-marrow micronucleus assay (Shelby et al., 1989), inducing an approximately 20-fold increase in the frequency of micronucleated polychromatic erythrocytes. In another study, treosulfan induced micronuclei in mouse bone-marrow, and peripheral blood cells (Gulati et al., 1990).

4.3 Synthesis

Treosulfan is carcinogenic via a genotoxic mechanism.

5. Evaluation

There is sufficient evidence in humans for the carcinogenicity of treosulfan. Treosulfan causes acute myeloid leukaemia.

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

Treosulfan is carcinogenic to humans (Group 1).

References

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