



Procedure for Working with Temozolomide

April 2010

Introduction

Identification

Common Name: Temozolomide, Temodar

Chemical Names:

8-carbamoyl-3-methylimidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one

3-Methyl-4-oxo-8-imidazo[5,1-d][1,2,3,5]tetrazinecarboxamide

8-Carbamoyl-3-methylimidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one

4-Methyl-5-oxo-2,3,4,6,8-pentazabicyclo[4.3.0]nona-2,7,9-triene-9-carboxamide

CAS Number: 85622-93-1

Usage/Bioactivity

Temozolomide (TMZ), is an antineoplastic agent that acts through its degraded biological form MTIC (5(3-methyl-1-triazeno)imidazole-4-carboxamide). MTIC degrades into the DNA methylating agent methyl diazonium that alkylates the DNA in tumour cells. It is approved by the FDA to treat 2 types of brain tumour – glioblastoma multiforme and anaplastic astrocytoma. TMZ has been shown to be mutagenic in vitro, and a related chemical Dacarbazine that also produces MTIC in vivo is considered as a Class 2B carcinogen (sufficient evidence of carcinogenicity in animals) by IARC (the International Agency for Research on Cancer). As a result of the above, and through the application of the precautionary principle, TMZ should be treated as a carcinogen by those working with it.

Toxicity

The lowest reported orally administered non-lethal toxic dose in humans was 18.75 mg/kg over 5 days. The effect seen was gastrointestinal. The lowest published lethal dose is 125mg/kg in the mouse delivered intraperitoneally. TMZ is also a mild skin and respiratory irritant.

Routes of Exposure

TMZ is readily absorbed orally, and via inhalation. Skin absorption can be effected by using an ester of TMZ in DMSO, however TMZ appears to have limited bioavailability via the skin (rat skin – 20 nano mol per cm² over 500 minutes).



The quantities of material used in the lab are typically very small, and thus with adequate precautions, it is unlikely that a lab worker would be exposed to enough TMZ to reach a toxic dose. The following represents the precautions that should be taken to minimize exposure. Note that for a carcinogen exposure should be reduced to as low as reasonably possible.

Precautions to be Followed

Preparation of solutions

All usage of powdered TMZ should occur in a properly functioning and tested fume hood. Where possible an outsourced solution should be used in place of a solid to avoid exposure to the airborne solid.

Usage of Solution

In addition to the PPE listed below, solutions of TMZ should be used with precautions designed to prevent accidental injection. When injecting into animal subjects, needle guards should be used as well as any restraint or sedation required for the relevant animal species to ensure that accidental injection does not occur.

Personal Protective Equipment (PPE)

At all times impermeable gloves, and lab coat should be used with TMZ. Lab coats should be washed regularly to ensure that there is no buildup of TMZ that will result in a chronic exposure. This is particularly important in light of the unknown carcinogenic potency of this compound.

Worker Hygiene

All workers should wash face and hands/arms with soap and water after working with TMZ. There should be no eating, drinking or chewing in the lab.

Animal Bedding

Workers should use regular precautions when dealing with soiled animal bedding, including gown, shoe covers, gloves and N95 respirator. TMZ is largely excreted in the urine in rats with 65-75% of the dose being eliminated in the first 24 hours post-exposure.



References/Further Information

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Temozolomide search performed on the Chemical Carcinogenesis Research Information System (CCRIS), a database of the National Library of Medicine's TOXNET system (<http://toxnet.nlm.nih.gov>), accessed April, 2010.

FDA Approval for Temozolomide from U.S. National Cancer Institute, NIH, <http://www.cancer.gov/cancertopics/druginfo/fda-temozolomide>, accessed April, 2010

Temozolomide MSDS (Fluka 76899), Sigma-Aldrich Canada, Version 3.1, Revision Date 03/25/2009, accessed April, 2010 at Sigma-aldrich.com