

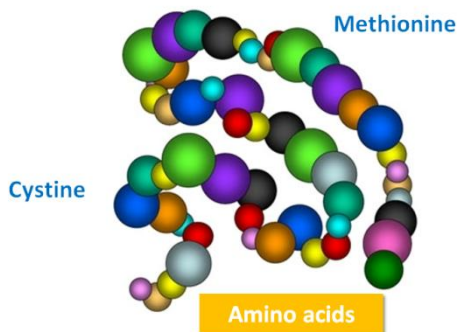
# SULPHITE OXIDASE AND MOLYBDENUM COFACTOR DEFICIENCY

## WHAT IS SULPHITE OXIDASE DEFICIENCY?

Sulphite oxidase deficiency is a congenital error of the metabolism of the sulfur amino acids which cause an **accumulation of sulphite in biologic fluids and tissues**. It may be caused by a deficiency in the sulphite oxidase enzyme or by a defect in the synthesis of the cofactor of such enzymatic reaction, the molybdenum cofactor (MoCo). In either case, a severe neurologic disease is the result.

## WHAT ARE SULFUR AMINO ACIDS?

Amino acids are **compounds that derivate from proteins**. Some of them (i.e.: methionine and cystine) contain sulfur groups and they form and degrade through the same metabolic pathway, the final function of which is to transform the sulphites into sulphates that are subsequently excreted through urine.

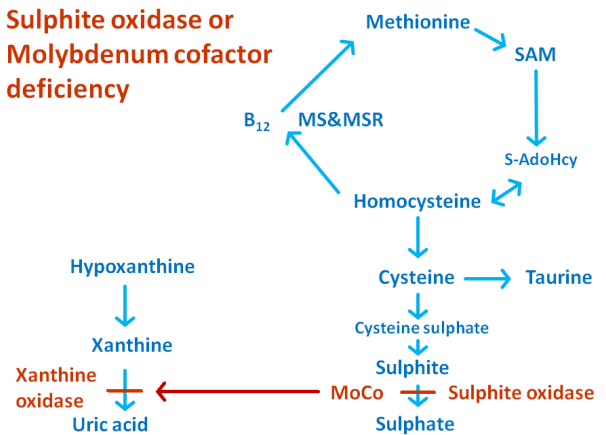


## WHAT IS THE FUNCTION OF SULPHITE OXIDASE?

Sulphite oxidase **transforms sulphites into sulphates** with the aid of molybdenum cofactor (MoCo), a molybdopterin. This cofactor is also indispensable for the function of two other enzymes, **xanthine oxidase** and **aldehyde oxidase**.

A deficiency in the Molybdenum cofactor will therefore cause a deficiency in all three enzymes as well, with all their clinical and biochemical consequences.

## Sulphite oxidase or Molybdenum cofactor deficiency



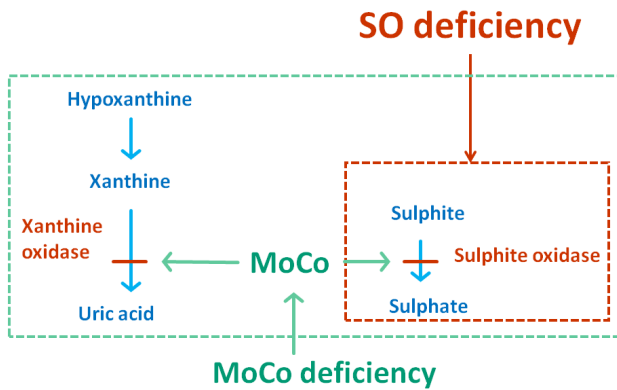
## WHAT DOES A METABOLIC ERROR OF SULPHITE OXIDASE MEAN?

When there is an alteration (error) in the metabolism (set of enzymatic reactions that make life), some metabolic processes do not occur with due effectiveness, which may cause the **accumulation of compounds that can be toxic to our organism** (such as sulphites, which are probably neurotoxic). These alterations have pathological consequences.

## WHAT HAPPENS IN SULPHITE OXIDASE DEFICIENCY?

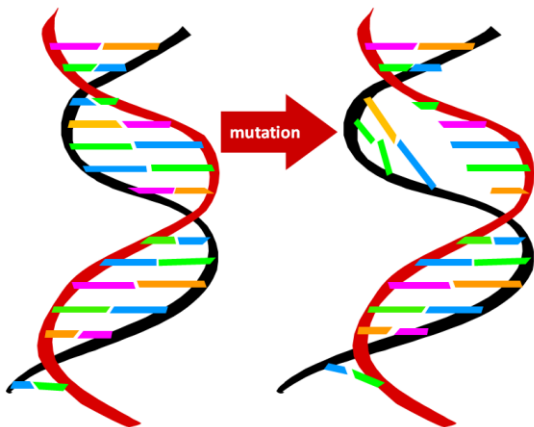
In sulphite oxidase deficiency, there is an **accumulation of all sulphites** which cannot turn into sulphates in order to be eliminated by the urine. If a molybdenum cofactor deficiency occurs, the three enzymes that are dependent on it fail and the result is an **accumulation of xanthine and hypoxanthine**. Moreover a **uric acid deficiency** develops.

will suffer from sulphite oxidase deficiency or hereditary molybdenum cofactor disorder.



## WHAT CAUSES SULPHITE OXIDASE DEFICIENCIES?

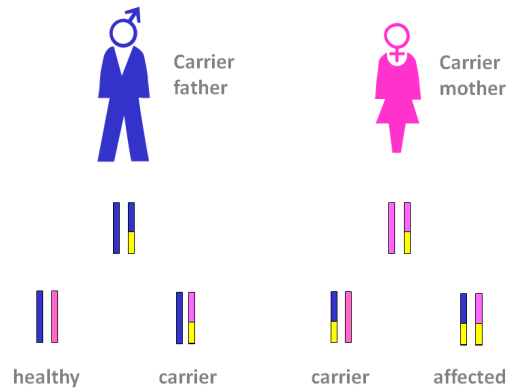
Each one of the reactions of metabolism that are going to give rise to the compounds that make up our body is determined genetically (codified). We all inherit either the correct or altered information from our parents, which gives our body the ability to carry out each of these metabolic processes.



A deficiency of sulphite oxidase activity occurs due to **mutations** (stable and hereditary changes) in the **SUOX gene** (protein coding) which **codifies this enzyme**. The deficiency can also be caused by **mutations in the several genes involved in the synthesis of cofactor MoCo**.

These deficiencies are **autosomal recessive hereditary disorders**, meaning that the parents are carriers of the mutation in this gene even though they do not suffer from the effects of this enzymatic deficiency. If both parents transmit a mutation to their offspring, the child

## Autosomal recessive inheritance



## WHAT HAPPENS WHEN A CHILD IS BORN WITH SULPHITE OXIDASE OR MOLYBDENUM COFACTOR DEFICIENCY?

The first manifestations in both deficiencies can develop **during the very first days of life or throughout the first year of the child's life**.

The clinical manifestations for sulphite oxidase deficiency are neurologic for the most part. They consist in muscle tone alterations, convulsions, movement (range of motion) disorders. In patients that have reached childhood, the symptoms include development delay and luxation of the crystalline lens. A lesion involving cerebral tissue may develop early in the disease.

### Clinical symptoms of sulphite oxidase deficiency



### Clinical symptoms of MoCo deficiency

In general, disease progression is fast and fatal, although there are some exceptions.

In molybdenum cofactor deficiency, xanthine accumulation causes kidney stones due to xanthinuria.

## HOW ARE SULPHITE OXIDASE AND MOLYBDENUM COFACTOR DEFICIENCY DIAGNOSED?

Diagnosis consists in an **analysis of the patient's urine and blood**. The plasma displays a rise in sulphocysteine and taurine as well as a total lack of cystine and homocysteine. Recent urine displays a rise in sulphites in addition to the alterations shown by the plasma.

In molybdenum cofactor deficiency, a lack of uric acid in serum and urine can be observed, as well as high excretion of xanthine and hypoxanthine in urine.

Confirmation of the disease requires **enzymatic and genetic studies**, with subsequent genetic counseling and prenatal diagnosis.

### Diagnosis of SO and MoCo deficiency



#### Clinical suspicion?

#### Biochemical study



↑sulphocysteine    ↑sulphite            ↓ SO  
 ↓cysteine, Hcy    ↑sulphocysteine  
 ↑taurine            ↑xanthine (MoCo)  
 ↓uric acid

#### Genetic study



*SMOX* or  
 MoCo genes  
 mutations

## WHAT ARE THE THERAPEUTIC OPTIONS FOR SULPHITE OXIDASE AND MOLYBDENUM COFACTOR DEFICIENCIES?

Therapeutic options are scarce in the case of single sulphite oxidase deficiency. In molybdenum cofactor deficiency, there are two possible options:

- Restriction of protein** with a diet low on methionine and supplemented with Cystine.
- Dextromethorphan**, an inhibitor of the NMDA receptor, to limit excitotoxicity.

Currently, an **experimental treatment with cyclic pyranopterin monophosphate (cPMP)** is available for patients with MoCo deficiency type A (caused by a mutation in the *MOCS-1* gene). cPMP is deficient in MoCo deficiency type A and it is the first intermediary in the synthetic pathway of MoCo. Implementing this substrate, activities of the MoCo depending enzymes can be restored leading to an amelioration of the neurodegeneration.

### Treatment of MoCo deficiency

Protein restriction + special formula  
(↓Met & ↑Cys)



Dextrometorphan (NMDA inhibitor)



Substrate replacement therapy: cPMP, for MoCo type A

Sulfite oxidase deficiency and MoCo deficiency are neurometabolic diseases that involve serious consequences. Early diagnosis and symptomatic treatment can help these patients.

### Translation

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