Sulfite: Here, There, Everywhere

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Inadvertent Exposures

Combustion of fossil fuels, Air pollutant

Large quantities as sulfur dioxide are expelled from volcanos

Kilauea on the Big Island

Small quantities endogenously formed in mammals from sulfur-containing amino acid metabolism
Deliberate Exposures

As Preservative-

Wine, Beer (dates to Roman times From burning sulfur candles)

Fruits and Vegetables (reduce browning, extend shelf-life)

Pharmaceuticals¹

Reductant - Antioxidant - Antimicrobial
What are Sulfites?

Oxidized Forms of the Sulfur Atom

Sulfur Dioxide, MW = 64, bp = -10°C (gaseous)

Sulfur (IV) - Oxidation state of 4

S = Atomic number 16 – electrons/shell, 2,8,6
Sodium Dioxide Readily Hydrates

**Sulfur Dioxide**
(irritant)

![Diagram of sulfur dioxide and water reaction]

**Sulfurous acid**

- Low pH: Forms radical
- High pH: Doesn’t form radical

**Bisulfite anion**

- Low pH: Forms radical
- High pH: Doesn’t form radical

**Sulfite dianion**

- Forms radical

**Carbon dioxide**

![Diagram of carbon dioxide and water reaction]

**Carbonic acid**

- Forms radical

**Bicarbonate anion**

- Doesn’t form radical

**Carbonate dianion**

- Doesn’t form radical
**Bisulfite Can Combine with $\text{SO}_2$ to form Metabisulfite**

\[
\text{SO}_3^2^- + \text{SO}_2 \xleftarrow{} \text{SO}_4^2^- \\
\text{Bisulfite (excess)} \quad \text{Metabisulfite (disulfite, pyrosulfite)}
\]

“Sulfite” usually added to drugs as sodium or potassium salts of:

**Sulfite, Bisulfite, or Metabisulfite**
Endogenous to Mammals

Small quantities formed from sulfur-containing amino acid metabolism - cysteine, methionine

\[ \text{Sulfite} + \text{H}_2\text{O} \rightarrow \text{Sulfate} + 2\text{H}^+ + 2\text{e}^- \]

Rapidly detoxified by sulfite oxidase (SOX) to form sulfate – a two electron oxidation, molybdenum dependent
Two Confirmed Sulfite Toxicities

Neurological abnormalities from genetic sulfite oxidase deficiency

Allergic reactions from exogenous exposure

Oral, parenteral, inhalational exposure: dermatitis, urticaria, flushing, hypotension, abdominal pain and diarrhea to life-threatening anaphylactic and asthmatic reactions

“The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people." - FDA Prevalence – 3-10% are sulfite sensitive among asthmatic subjects.
Sulfite Radical Causes Significant Reactivity

“Sulfite is a double-edged sword with their antioxidant as well as prooxidant properties”

\[ \text{HSO}_3^- + \text{O}_2 \rightarrow \text{HSO}_3^- + \text{1 e}^- \]

Radical formation is a one electron oxidation
Auto-oxidizes with oxygen
Prooxidant in presence of oxygen
Detectable by \text{EPR}\textsuperscript{6}

(radical readily forms in aqueous in presence of oxygen)
Sulfite Can React in/with Drug Formulation Components (our work)

Propofol emulsion with sodium metabisulfite – EPR radical readily detected upon opening to air. Causes reaction with propofol.

Morphine with sodium bisulfite–EPR trapping also readily detected radical upon opening. Causes morphine -sulfite adduct formation.
Sulfite Can Oxidized Propofol in the Presence of Emulsion Lipids

Propofol + Emulsion lipid + Metabisulfite

Air exposure

Propofol Dimer
Sulfite Content of Some Drugs

10 ppm = 10 mg/kg, 0.01 mg/ml
Lab Results Show Activity in Biological Systems

Sulfite radical is formed endogenously

1. Sulfite induces protein oxidative damage in granulocytes - (Bi)sulfite oxidation catalyzed by a myeloperoxidase (MPO)-H$_2$O$_2$ system results in the formation of highly reactive sulfite-derived radicals$^{10}$

Sulfite increases neuronal excitation

2. Voltage-gated Na$^+$ current (INa) was stimulated, and current inactivation and deactivation were slowed in SMB-treated (30 μM) neurons$^{5,9}$

3. Pilocarpine-induced seizures were exacerbated, and acute neuronal damage and chronic mossy fiber sprouting increased in sodium metabisulfite-treated rats$^9$
Conclusion

Sulfite-containing drugs should be used as second choice

Drugs with non-sulfite preservatives are available

Parabens, phenol, benzyl alcohol, benzoates

Preservative-free formulations available

Dr. Baker has no financial interests in the products in this presentation

2. Scientific Opinion on the re-evaluation of sulfur dioxide (E 220), sodium sulfite (E 221), sodium bisulfite (E 222), sodium metabisulfite (E 223), potassium metabisulfite (E 224), calcium sulfite (E 226), calcium bisulfite (E 227) and potassium bisulfite (E 228) as food additives. *EFSA Journal*, 2016;14:4438 Vally H, Misso LA, Madan V. Clinical effects of sulphite additives. *Clin Exp Allergy*, 2009; 39, 1643–1651


Supplemental Information
Sulfite Regulation and Warnings

Sulfite is categorized as Generally Regarded as Safe (GRAS) by FDA

1986 - FDA prohibited the use of sulfites on fruits and vegetables to be served raw or presented fresh to the public - timbo

FDA - If content over 10 ppm (or 10 mg/kg) “a detectable amount” – requires label “Contains Sulfites”

All prescription drugs with sulfite (except epinephrine for allergy or emergency situations) should have a FDA specific allergy-type reaction warning statement
FDA
Required Warning Statements of Prescription Drugs Containing Sulfites

The labeling required by 201.57 and 201.100(d) for prescription drugs for human use containing a sulfite, except epinephrine for injection when intended for use in allergic or other emergency situations, shall bear the warning statement:

"Contains (insert the name of the sulfite, e.g., sodium metabisulfite), a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people."

Title 21 – Food and Drugs, Chapter 1 – Food and Drug Administration, Subchapter C- Sec 201.22