Title: The Current State and Future Directions of Skeletal Toxicology: Forensic and Humanitarian Implications of a Proposed Model for the *In Vivo* Incorporation of Drugs into the Human Skeleton

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REVIEW ARTICLE

The Current State and Future Directions of Skeletal Toxicology: Forensic and Humanitarian Implications of a Proposed Model for the *In Vivo* Incorporation of Drugs into the Human Skeleton

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Highlights

- Published skeletal toxicology case studies and experiments are reviewed
- A novel model for the incorporation of drugs into bone is proposed and detailed
- Methodological considerations are raised by the novel model
- The model also suggests skeletal toxicology may aid humanitarian investigations
- Nerve agent pharmacokinetics are discussed in relation to bone chemistry

ABSTRACT: At present, the inability to meaningfully and reliably conduct toxicological testing on human skeletal material represents a significant gap in forensic practice, especially in a time when the U.S. has declared opioid use a public health emergency and chemical weapon use in both mass and isolated attacks is prevalent in international news. In recent years, an increasing number of case studies and experiments have been published in an attempt to fill this knowledge gap. These papers are reviewed, and their valuable and pertinent findings discussed. However, the lack of an established model for the incorporation of drugs of forensic interest into bone has limited interpretation of results and delayed adoption of skeletal toxicology methods into accepted forensic practice. A model for the *in vivo* incorporation of drugs of forensic interest into bone tissue is proposed herein. This model is derived from known pathways for *in vivo* incorporation of compounds and analytes not of traditional forensic interest into bone tissue and is based on principles of ionic exchange, adsorption, and substitution. Testing and understanding these pathways may better guide skeletal toxicological experimentation, resulting in methods more tailored to human bone as a unique, largely inorganic matrix, as well as in increased interpretability of results. Further, the proposed model suggests possible novel applications for the field of skeletal toxicology on the humanitarian stage. Indeed, based on their chemical properties, chemical weapon nerve agents should be investigated as xenobiotics that may incorporate into the human skeleton at relatively elevated levels. If nerve agents can be isolated from skeletal remains, the field of skeletal toxicology may be able to offer important contributions to human rights investigations of mass graves.