

What does it mean?

Simulated gastric hydrolysis and developmental toxicity of dioctyltin bis(2-Ethylhexylthioglycolate) [DOTE] in rabbits and mice¹

Richard D. Costlow, Hans Nasshan, Peter Frenkel, (2017). *Simulated gastric hydrolysis and developmental toxicity of dioctyltin bis(2-Ethylhexylthioglycolate) [DOTE] in rabbits and mice. Regulatory Toxicology and Pharmacology*

Substance: Dioctyltin bis(2-ethylhexylthioglycolate) (DOTE; CAS 15571-58-1)

Study type: Simulated gastric hydrolysis + prenatal developmental toxicity studies in rabbits and mice (OECD TG 414, GLP)

Purpose: To determine whether DOTE forms dioctyltin dichloride (DOTC) in the stomach and whether DOTE causes developmental toxicity².

1. Background and regulatory context

Multiple dioctyltin compounds have raised regulatory concern for developmental toxicity based on **read-across** data from dioctyltin dichloride (DOTC) and related dialkyltin chlorides. These concerns assume that DOTE may hydrolyse in the stomach to form **dioctyltin dichloride**, which is considered the toxicologically relevant breakdown product.

For DOTE, this assumption had not been adequately tested using modern analytical methods or guideline-relevant developmental toxicity studies. The present work was conducted to directly examine gastric hydrolysis behaviour and to assess potential maternal and developmental toxicity in two laboratory species.

2. Key questions addressed

- Does DOTE convert to dioctyltin dichloride (DOTC) under stomach-like conditions?
- Do gastric hydrolysis products of DOTE cause maternal or developmental toxicity when administered orally during pregnancy?

¹ [“Simulated gastric hydrolysis and developmental toxicity of dioctyltin bis\(2-Ethylhexylthioglycolate\) \[DOTE\] in rabbits and mice” - ScienceDirect](#)

² Developmental toxicity is defined as the study of adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation (US EPA 1991)

- Is read-across from DOTC to DOTE scientifically justified for hazard identification?

3. Simulated gastric hydrolysis³

- DOTE exposed to acidic conditions representative of the mammalian stomach (pH 1.2, 37°C for 120 hours).
- The study used ¹¹⁹Sn-NMR, which directly detects tin-containing species allowing unambiguous detection of DOTC if formed.
- Results:
 - DOTE did not convert to dioctyltin dichloride (DOTC) under simulated gastric conditions.
 - Instead, partial ligand exchange occurred, resulting in mono-chloro thioglycolate species rather than the dichloride.
 - DOTC was not detected at analytically relevant levels.
- Regulatory relevance: These findings do not support the assumption that DOTE generates the known dioctyltin chloride toxophore in the stomach. As a result, read-across from DOTC to DOTE for developmental toxicity is not mechanistically supported.

4. Prenatal developmental toxicity studies

Developmental toxicity was evaluated in both rabbits and mice, two species commonly used in regulatory reproductive toxicity testing. Pregnant animals were administered DOTE during the critical periods of pregnancy. The doses administered to rabbits were 0, 4, 20, and 80 mg/kg bw/day on gestation day 5 to 29. The doses administered to mice were 0, 15, 30, and 60 mg/kg bw/day on gestation day 5 to 17. Maternal health, pregnancy outcomes, and foetal development were assessed using standard guideline-type endpoints.

- Maternal findings
 - No treatment-related maternal mortality occurred.
 - No adverse effects on clinical condition, body weight, or pregnancy maintenance were observed that could be attributed to DOTE or its hydrolysis products.

³ Simulated gastric hydrolysis of chemicals is an in vitro (laboratory-based) procedure designed to mimic the digestive processes of the human stomach—specifically the breakdown of chemical compounds (drugs, food components, or nutrients).

- Developmental findings
 - No treatment-related effects on implantation, foetal survival, litter size, or sex ratio were observed.
 - No effects on foetal growth or development were identified.
 - No increase in external, visceral, or skeletal malformations was observed.
 - Any foetal findings were sporadic, non-dose-related, and within historical control ranges.
- NOAELs
 - Maternal No Observed Adverse Effect Level (NOAEL)⁴: At or above the highest dose tested
 - Developmental No Observed Adverse Effect Level (NOAEL): At or above the highest dose tested

5. Overall regulatory conclusion

- DOTE does not hydrolyse to dioctyltin dichloride under simulated gastric conditions.
- **Gastric hydrolysis products of DOTE did not cause maternal toxicity or developmental toxicity in rabbits or mice.**
- The developmental toxicity profile of DOTE is distinct from that of DOTC.

6. Implications for read-across and classification

- Read-across from DOTC to DOTE is not supported by gastric hydrolysis data or in vivo developmental toxicity studies.
- DOTE **does not** generate the chloride species considered responsible for developmental effects found with DOTC.
- Based on substance-specific experimental evidence, **classification of DOTE as a reproductive or developmental toxicant is not supported** under standard hazard classification frameworks (e.g., EU CLP / GHS).

⁴ Highest dose at which there was *not* an observed toxic or adverse effect.

7. Regulatory significance

These studies provide direct, substance-specific evidence addressing both metabolic behaviour under gastric conditions and in vivo developmental toxicity. The results demonstrate that prior hazard assumptions based solely on structural analogy to DOTC are not scientifically justified for DOTE. The study data from two toxicology studies conducted per OECD Test Guideline 414 and GLP principles support a conclusion of no developmental hazard following oral exposure and are relevant for risk assessment and classification decisions.

About GOSC

The [Global Organotin Stewardship Council](#), established in 2021, aims to enhance understanding of the intrinsic health and environmental properties of organotin compounds while highlighting their benefits. It actively communicates this information to stakeholders, ensuring scientific consistency and clarity.

Additionally, GOSC represents the major organotin manufacturers and technology sector in order to support Members and market organizations in their engagement globally with policy makers and regulatory authorities. The Global Organotin Stewardship Council (GOSC) consists of manufacturers of organotin manufacturers: Galata Chemicals, Gulbrandsen, Nitto Kasei Co., Ltd., PMC Group, Reagens S.p.A, Songwon Industrial Group, and TIB Chemicals AG.

GOSC monitors and responds to global Regulations on Organotins with the following objectives:

- Develop scientific and socioeconomic data to accurately assess organotin-based substances.
- Demonstrate that organotin-based substances can be safely handled.
- Assess if Organotin-based substances are easily replaced in the applications in which they are used and where they show outstanding performance or are critical in certain applications.
- Recommend justifiable regulatory action and/or appropriate risk management measures for organotin based substances.
- Promote the most appropriate regulatory management option for any initiative that may be triggered on organotin-based substances and develop regulatory consensus on it.

