

1) Carcinogenicity

The French Competent Authority proposes a harmonized classification for TODI as Carc. 1B. Since there is no experimental data available on the carcinogenic potential of TODI, the Carc. 1B proposal is based on a read across approach from the diamine TODA (classified as Cat. 1B carcinogen) to the diisocyanates TODI assuming that 'TODI will be totally metabolized in TODA in organisms'.

Freudenberg Sealing Technologies GmbH is of the opinion that the read across is scientifically not justified and disagrees with the classification proposal for Carc. 1B.

Data on in vivo metabolism in animals for the very similar diisocyanate MDI shows that after inhalation exposure no free diamine MDA is formed [1,2].

Since no hydrolysis studies are available in which MDI and TODI have been examined in parallel, Freudenberg Sealing Technologies GmbH has performed a hydrolysis study in an ISO 9001 certified test facility to compare the hydrolysis behavior of MDI and TODI (report can be provided upon request [3]). The study was performed at 37°C and pH 7. The initial concentration of test item in the buffer solutions was 5 µg/mL with 1% acetonitrile. Samples were directly injected and analyzed using a HPLC method. For each assay, the start time point for measurement was made as quickly as the sample could be loaded into the HPLC system and analyzed (3 to 5 minutes). The $t_{1/2} \pm 2 \sigma$, determined from replicate measurements at pH 7 and 37 °C, ranged between 4.0 and 5.8 hours for TODI and 3.1 and 10.1 hours for MDI. The wider $t_{1/2}$ range in case of MDI is due to the fact that less data points lie within the hydrolysis range of 30-70 % in comparison to TODI. Complete hydrolysis of TODI and MDI was obtained after 1692 min and 1415 min, respectively. The new data demonstrate a comparable hydrolytic behavior of TODI and MDI in buffer systems.

The common postulated mechanism for MDI's carcinogenicity is via a non-genotoxic effect, oncogenesis on basis of irritation, inflammation and increased cell proliferation [4]. A similar mechanism of carcinogenicity is anticipated for TODI when compared to the structurally very similar MDI. MDI is classified for Carc. 2, but not for mutagenicity, whereas its hydrolysis product MDA is classified for Carc. 1B and Muta. 2. Based on the different classification and the fact that free MDA has never been detected in vivo after MDI application, the in vivo behaviour of MDI cannot be simply described by the hydrolysis to MDA as the newly available hydrolysis data in a buffer system would suggest. Thus, hydrolysis data in buffer systems cannot be used to justify a read across from diamines to the respective diisocyanates. Similar reactivity is anticipated for TODI and MDI from structural comparison and hydrolysis data. Consequently, read across from TODA to TODI is scientifically not sound, whereas the read across from MDI to TODI is justified.

In conclusion, Freudenberg Sealing Technologies GmbH proposes a harmonized classification and labelling as Carc.2 for TODI based on the read across to the structurally very similar MDI.

References:

[1] CoRAP Substance Evaluation Report, 4,4'-methylenediphenyl diisocyanate (MDI), EC No 202-966-0, November 2018

[2] CoRAP Substance Evaluation Report, m-tolyldiene diisocyanate (TDI), EC No. 247-722-4, November 2013

[3] Prüfbericht FTI-Auftragsnummer 802505, Freudenberg Technology Innovation SE& Co. KG, 15.05.2020

[4] EU Risk Assessment Report, 3rd Priority List, Volume 59, 4,4'-methylenediphenyl diisocyanate (MDI), Joint Research Center, 2005