

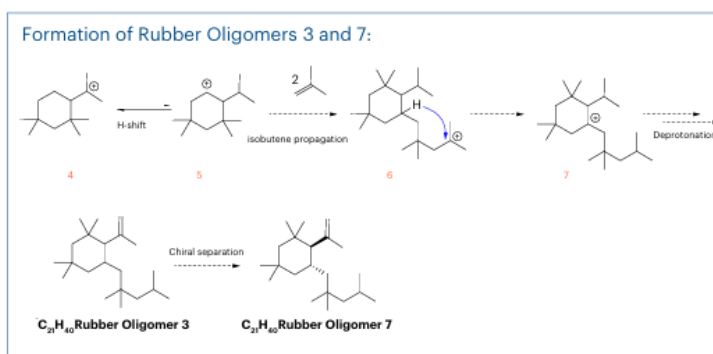
## ICH Q3E: Monograph for rubber oligomer C<sub>21</sub>H<sub>40</sub>

The draft ICH Q3E Guideline for Extractables and Leachables, Supporting Documentation, Class 3 Leachable Monographs, dated 2025-08-18, contains information on rubber oligomer C<sub>21</sub>H<sub>40</sub>. The good news is, that the derived PDE is quite high (acute parenteral 10.000 ug/day, chronic parenteral 1.000 ug/day).

I just wonder why this chapter mentions a specific diastereomer (cis isomer) of the rubber oligomer C<sub>21</sub>H<sub>40</sub>, even though the rubber oligomer commonly found in rubber extracts is a mixture of the cis- (CAS 114123-73-8) and trans- (CAS 114123-74-9) isomers. This mixture is known as rubber oligomer 3, CAS 2512216-71-4, and is available, for example, as a USP reference standard. The NMR data provided by the USP, the data given by Piet Christiaens [1] as well as my own NMR studies on rubber extracts, clearly indicate the presence of a diastereomer mixture rather than a single, specific diastereomer.

On the other hand, in its technical guide to rubber oligomers [2], the USP provides a scheme for the formation of rubber oligomer C<sub>21</sub>H<sub>40</sub>, which shows a step from rubber oligomer 3 (the mixture of diastereomers) to rubber oligomer 7 (the trans diastereomer, CAS 114123-74-9). They do not cite any literature, and it is unclear to me whether they mean to say that the conversion of the mixture to trans in rubber is plausible, or only generally that chiral separation, e.g., by chromatographic methods, is possible.

**Formation of Rubber Oligomers 3 and 7:** Rearrangement of carbocation in compound-4 with H-shift gives intermediate-5. Then reaction with 2 moles of isoprene units gives intermediate-6. Rearrangement of carbocation in intermediate-6 gives cyclic tertiary carbocation-7. Finally, H-shift and followed by loss of proton results in the formation of Rubber Oligomer 3.



Some suppliers of rubber oligomer standards offer the isolated trans isomer C<sub>21</sub>H<sub>40</sub> (rubber oligomer 7), and one of them also offers all isolated isomers, not just the cis and trans diastereomers, but all 4 enantiomers.

With all due respect for their scientific efforts (chiral separation can be quite challenging), what is the advantage of using isolated stereoisomers of the rubber oligomer C<sub>21</sub>H<sub>40</sub>, since these are not normally separated by the GC-MS methods used in E&L studies?

I would like to ask the E&L experts if they have ever observed the occurrence of an isolated diastereomer of the rubber oligomer C<sub>21</sub>H<sub>40</sub> in their E&L studies and what their general opinion is on the use of specific stereoisomers of C<sub>21</sub>H<sub>40</sub> as analytical reference standards.

Another topic is the structural isomers (not stereoisomers) of the halogenated rubber oligomers C<sub>13</sub> and C<sub>21</sub>. They occur mainly as allyl isomers, but also as vinyl analogues (further subdivided into E and Z isomers). These compounds can be separated using standard GC-MS methods, and due to their different properties (e.g., protein binding reactivity of allyl isomers, no reactivity of vinyl

isomers), the identification of these less harmful compounds using reference standards is advantageous.

In 2023, I already uploaded an article on this topic. It can be viewed here:

[https://www.researchgate.net/publication/375863987\\_Optical\\_isomers\\_diastereomers\\_of\\_rubber\\_oligomer\\_C21H40](https://www.researchgate.net/publication/375863987_Optical_isomers_diastereomers_of_rubber_oligomer_C21H40)

[1] (Halo)butyl Oligomers in Pharmaceutical Rubbers, PDA Conference 2013, Prague, Piet Christaens

[2] <https://www.usp.org/sites/default/files/usp/document/products-services/rubber-oligomers-technical-guide.pdf>