Final Concept Paper
Q3C (R10): Impurities: Guideline for Residual Solvents
Dated 26 November 2024
Endorsed by the Management Committee on 06 January 2025

1. Type of Harmonisation Action Proposed

The Q3C Expert Working Group (EWG) is revising monographs already listed in the support documents or Parts II - VI of the guideline as new data become available. In addition, the EWG will re-structure the document, i.e. to compile all compound specific monographs into one separate monographs document separated from the main guideline and link both documents.

2.1 Statement of the Perceived Problem

Permitted Daily Exposures (PDEs) for N,N-Dimethylformamide (DMF), Dichloromethane (DCM) will be revisited based on changes in risk classification classes for mutagenic/carcinogenic risk of these substances by IARC/ECHA and for Ethyleneglycol (EtG) based on an assessment of NTP published after finalization of the respective monograph. The ICH Q3C Guideline was finalised in 1997. Monographs for specific residual solvents listed in tables in the parent guideline were not published but are available as support documents at ICH. In later maintenance cycles monographs for additional residual solvents were prepared and added as Parts II - VI continuously at the bottom of the guideline. In 2019 the first monographs contained in the not published support documents were made publicly available as a zip folder for download. This makes it very cumbersome for users to find solvent specific monographs included in the tables in the parent guideline. The EWG proposes to compile all solvent specific monographs into one separate addendum document linked to the specific table in the parent guideline where the specific solvents are listed with their PDE values.

2.2. Background to the Proposal

- IARC has reclassified DMF from class 2B “possibly carcinogenic to humans” to 2A “probably carcinogenic to humans”. This was driven by new data that may also change to current PDE for DMF. The EWG will evaluate the data foundation for the change of classification by IARC and if necessary will revise the monograph in Q3C. *IARC Some Industrial Chemicals, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 115 (2018).*

- ECHA reviews a proposal for re-classification of Dichloromethane from class Carc 2 to class Carc 1B and adds classification as Muta 2. This will classify Dichloromethane as a mutagenic carcinogen. Mutagenic carcinogens would be ICH Q3C class 1 solvents. The EWG will evaluate the data foundation for the change of classification by ECHA and if necessary will revise the monograph and classification in Q3C. *Proposal for Harmonised Classification and Labelling, Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2, Chemical name: dichloromethane, (2023)*
- The US National Toxicology Program assessed EtG in 2004, a few years after the current monograph was adopted. The assessment suggests different toxicology studies as more relevant for human risk and therefore for PDE calculation. *NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Ethylene Glycol. NIH Publication No. 04-4481 (2004)*

3. Issues to be Resolved

- Revising PDEs for DMF, DCM and EtG if new data support a change.
- Facilitate use of the guideline for applicants by making the structure clear and easy to find monographs for the solvents included in the guideline

4. Planning

Type of Expert Working Group

The current EWG is comprised of experts from each of the Founding Regulatory Members and from other ICH Members as appropriate, representing the necessary toxicological and quality expertise. Additionally, ICH Observers may participate on the EWG pending a favorable decision by the ICH Assembly. The focus of the EWG will primarily be safety assessment by toxicologists and document structure/formatting.

Timing

Agreement of Concept Paper by the Q3C EWG	Dec 2024
Adoption of Concept Paper by the ICH Management Committee	Jan 2025
Step 1 sign off of revisited/revised monographs/PDEs for DMF, DCM, EtG	Sep 2025
Step 1 sign off of re-structured guideline documents	Sep 2025
Step 2 a/b endorsement and release for public consultation	Oct 2025
Step 3 close of public consultation	Mar 2026
Step 3 documents and sign off	Sep 2026
Step 4 adoption	Nov 2026