FOREWORD

1. Project 4.97 to development of a Detailed Review Paper (DRP) on the Retinoid System was added to the Test Guidelines Programme work plan in 2015. The project was originally proposed by Sweden and later, the European Commission joined the project as a co-lead. In 2019, the OECD Secretariat was added to coordinate input from expert consultants. The initial objectives of the project were to:

- draft a review of the biology of retinoid signalling pathway,
- describe retinoid-mediated effects on various organ systems,
- identify relevant retinoid in vitro and ex vivo assays that measure mechanistic effects of chemicals for development, and
- in vivo endpoints that could be added to existing test guidelines to identify chemical effects on retinoid pathway signalling.

2. This DRP is intended to expand the recommendations for the retinoid pathway included in the OECD *Detailed Review Paper on the State of the Science on Novel In vitro and In Vivo Screening and Testing Methods and Endpoints for Evaluating Endocrine Disruptors* (DRP N° 178). The retinoid signalling pathway was one of seven endocrine pathways considered to be susceptible to environmental endocrine disruption and for which relevant endpoints could be measured in new or existing OECD Test Guidelines for evaluating endocrine disruption. Due to the complexity of retinoid signalling across multiple organ systems, this effort was foreseen as a multi-step process. This DRP is intended, in part, to be an initial scoping effort to identify retinoid signalling pathway test methods, markers, and endpoints for consideration. After expert group discussion of the technical aspects and regulatory context, the initial scoping effort may lead to recommendations for identification of early screening assays that could be included as a multi-tiered approach, identification and development of biomarkers to be used in studies of humans and wildlife, and endpoints that could be added to enhance exiting in vivo test guidelines. This effort was intended to be modelled after the thyroid scoping effort (GD N° 207).

3. The EU-Commission supported the first draft DRP development, through a contract with Brunel University and the sub-contractors Technical University of Denmark

4. The Retinoid DRP project was discussed at meetings of the Advisory Group on Endocrine Testing and Assessment (EDTA) in 2017 and 2018. The EDTA recommended narrowing the scope of the original proposal to focus the DRP on specific organ systems for which some information is known on the role of retinoid signalling. Sweden sent a request for experts to contribute to the drafting effort in 2017, but received few nominations. In response, specific experts identified at an earlier stage of this project contributed, as well as newly identified experts can be noted in the drafts prepared by Sweden.

5. At the 2018 EDTA meeting, Sweden presented drafts of a section reviewing the overall biology of the retinoid pathway and a section describing the role of retinoids on female reproduction. A third chapter on the male reproductive system was drafted in 2019.

6. The retinoid pathway signalling was also discussed at a 2017 European Commission workshop to identify gaps in current OECD Test Guidelines and prioritise new assays to bridge the gaps. The meeting attendees identified the development of retinoid pathway assays and endpoints for inclusion in OECD Test Guidelines as a high priority. As a result, the European Commission supported the drafting of two additional reviewing retinoid effects on central nervous system (CNS) and craniofacial/skeletal system development, also included in this DRP. Additional sections were organised by the OECD Secretariat and prepared by expert consultants. In Q2 2019, OECD circulated a request for updated nominations to the Expert Group on Retinoid Pathway Signalling and identified expert consultants for drafting.

7. Important to note: The chapters were drafted by different groups, the content of some sections was discussed extensively and revised several times prior to this version, while this is a very early draft of other sections. Sweden is currently finalizing the overview, the male and female reproductive chapters, and these sections are to be included in a Nordic Chemicals Report. The skeletal and CNS sections were developed in Q3 of 2019 are in a more nascent stage, but will benefit from input from a WNT written commenting round, along with input from the EDTA and OECD Expert Group on the Retinoid Signalling Pathway

8. Following the conclusion of the first commenting round, the draft DRP will be revised by the expert consultants based on the comments received. In addition, a face to face expert group meeting will be held in November 2019. The objectives of the meeting are to address any outstanding comments received during the first commenting round and to collate recommendation on possible next steps. The meeting discussion will be captured and added to the DRP as an additional chapter. The revised, complete draft will be circulated for a second WNT commenting round in 2020.