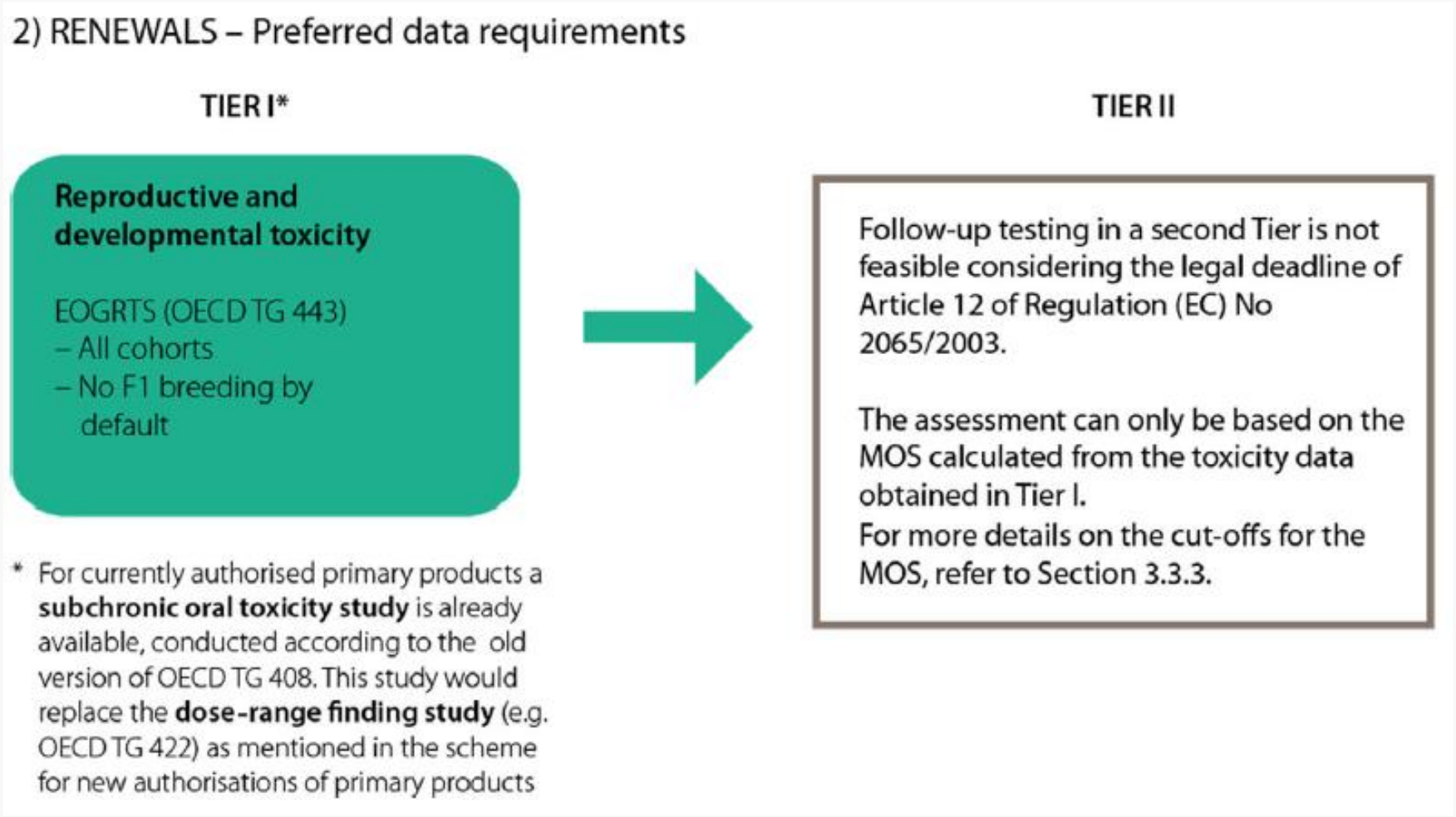
EFSA GUIDANCE ON SMOKE FLAVOURING PRIMARY PRODUCTS - RENEWALS

Manon Beekhuijzen

30 June 2021

charles river

TIERED APPROACH FOR RENEWALS - PREFERRED



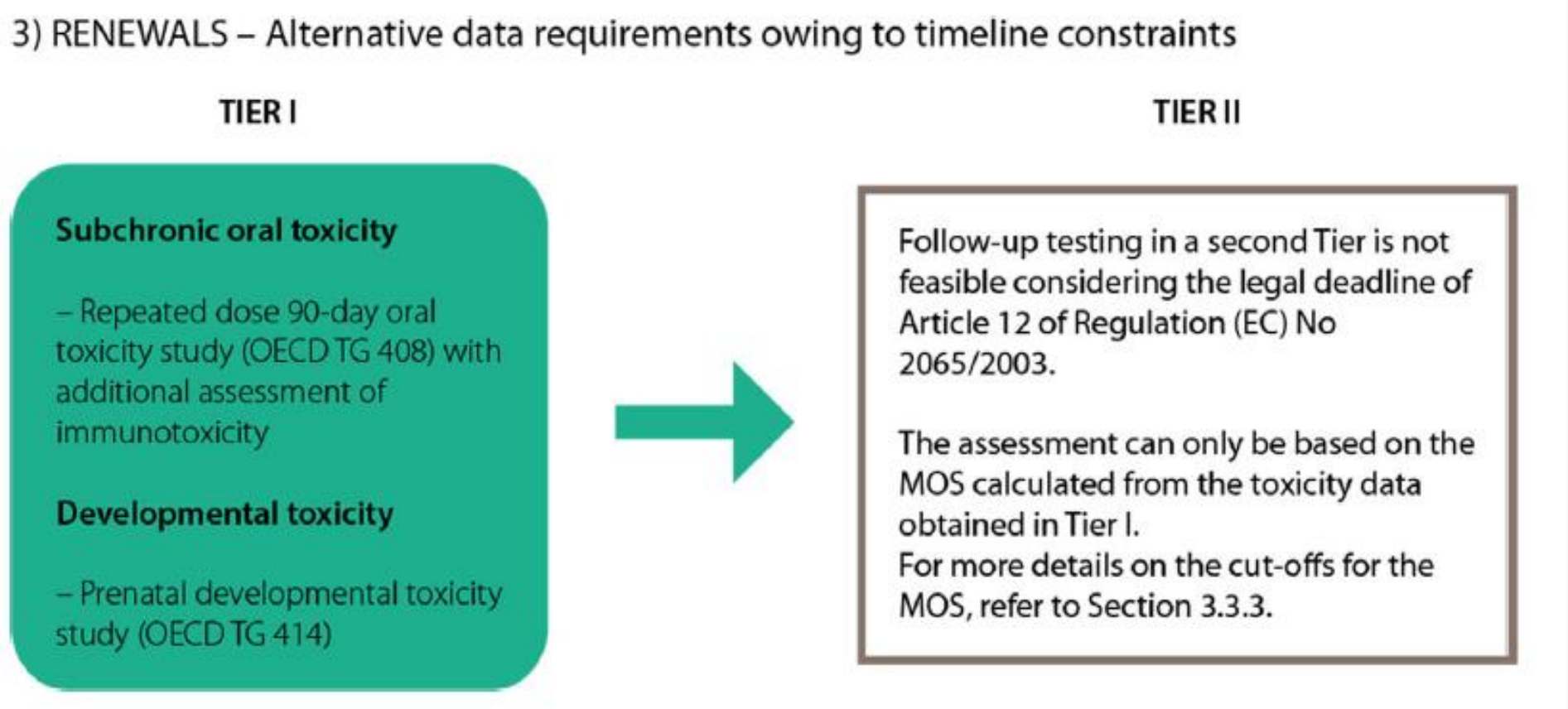
charles river

EOGRTS

Not possible to finish in time for June 2022 deadline

- An EOGRTS (with 2 weeks premating) takes 9 months from start until draft report. Finalization usually takes 3 months.
- Due to the high demand of studies, we are already fully booked for the rest of this year and part of next year.
- EOGRTS is a large study of which 4-8 can run per lab per year.

TIERED APPROACH FOR RENEWALS - ALTERNATIVE



charles river

EFSA 90-D STUDY WITH IMMUNOTOXICOLOGY

Not possible to finish in time for June 2022 deadline

- This study takes 7 months from start until draft report. Finalization usually takes 2 months.
- Needs huge investments in time, equipment and personnel.
- As there are still a lot of uncertainties, we have not started the implementations of the new assays and are awaiting more clarity before we hire extra personnel.
- We can only start this study every 2 months because the additional immunology endpoints to be included in OECD 408 would result in a profound increase in workload for immunology assays.

TIERED APPROACH FOR RENEWALS – PROPOSED ALTERNATIVE

Proposed by Charles River

- To improve chance of meeting the June 2022 deadline (can be performed and reported in 2022) for all compounds.
- The study design that we propose takes 7 months from start until draft report. Extremely important with this is that all labs that can perform an EOGRTS can also perform this design, and that is not the case for the EFSA 90-d immunotox study.
- No need to hire new personnel and develop/implement new techniques that are only applicable for a small number of compounds.
- Improve scientific evaluation as closer resemblance with EOGRTS (i.e. preferred data requirement).
- Includes methods already in place for standard regulatory studies, with extensive experience at CROs and ample available historical control data.

PROPOSED ALTERNATIVE STUDY DESIGN

Combined 90-d/repro screening study with extras

- 10 animals/sex/group
- Treatment from premating until PND 21 (at least 13 weeks)
- Includes all 90-d (OECD 408) parameters, repro screening (OECD 421) parameters, and extra endocrine disruption and immunotox parameters
- ED measurements: reproduction and postnatal development up to PND 21, oestrus cycle, sperm parameters, thyroid hormones (adult F0-animals, PND 4 and PND 21 pups), additional hormones (testosterone, FSH, LH, oestradiol)
- Additional immunotoxicology measurements: Bone marrow smear evaluation, plasma globulin[1], complement assays (C3 and C4), fibrinogen[2], immunophenotyping of splenocytes (T cells, B cells, NK cells, T helper cells and T cytotoxic cells), and TDAR[3]

[1] Plasma will be retained in order to measure immunoglobulin isotypes when unexplained changes in globulin are observed.

[2] Plasma will be retained in order to measure alpha-2-macroglobulin when an acute phase response is suspected based on changes in fibrinogen.

[3] TDAR can be performed as part of the main study (using satellite animals) or as separate study (possibly as dose range finding study)

And perform a developmental toxicity study (OECD 414) in the rat (as mentioned also for other alternative).

IMPORTANT NOTE

Number of animals (assuming 12 fetuses/pups per litter):

- OECD 443 = 1400
- EFSA 90-d + OECD 414 = 1224 (80 + 1144)
- CRL alternative + OECD 414 = 1784 (640 + 1144)

BACKUP SLIDES

Details

PROPOSED ALTERNATIVE STUDY DESIGN

Combined 90-d/repro screening study with extras versus 90-d toxicity study with immunotox

Not included:

- Phenotyping analysis of macrophages and T regulatory cells in the spleen (but done for all other cells: T cells, B cells, NK cells, T helper cells, and T cytotoxic cells)

Alternative:

- Immunoglobulin isotypes > Globulin will be measured of which the results could trigger immunoglobulins
- CRP > Fibrinogen will be measured of which results could trigger alpha-2-macroglobulin (which is a better alternative for CRP)
- TDAR (= standard in EOGRTS) instead of Natural killer cell functional analysis, Phagocytic activity test and Mitogen stimulation assays for B and T cells

Extras:

- Oestrus cycle
- Reproduction/fertility assessment
- Postnatal development until PND 21 (until weaning), including ED parameters