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SUSTAINABILITY

INNOVATION

FEED SAFETY

ANIMAL HEALTH AND WELFARE

SAFE FOOD

Meeting of EFSA, EC and FEFANA related to the evaluation of efficacy of feed additives of the functional group Physiological Condition Stabilisers, 16 June 2025

Physiological conditions stabilizers: 'PCS'
Objectives and consideration by FEFANA

The objective

<u>Enable authorisation of</u>: 'substances or, when applicable microorganisms, which, when fed to animals in good health, favourably affect their physiological condition, including their resilience to stress factors.'
(ref. Com. Reg. (EU) No 2019/962 amending Reg (EC) No 1831/2003).
These additives have the potential to help prevent, mitigate and/or reduce the impacts of unavoidable stress conditions encountered by animals during their life cycle.

The functional group of PCS is addressed in the EFSA Guidance on the assessment of the efficacy of feed additives of 2024. However, as PCS have a very specific functionality, including the resilience to stress factors, the current EFSA guidance does not provide specific endpoints, which can be used to demonstrate efficacy. This remains important because general endpoints for zootechnical additives such as weight gain and feed utilization (FCR) are not appliable here.

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Physiological conditions stabilizers: 'PCS'
Scientific rationale

- ✓ Stress factors activate the neuro-endocrine system, which is linked to the immune system, leading to a range of adverse impacts on animal health, resilience to diseases, and welfare.

- ✓ This cascade of physiological responses takes place in a comparable way under different stress scenarios in all animal species.

- ✓ In line with the EFSA guidance document of 2024 (Section 3.4.4.): three (non-exclusive) stress examples are social stress, metabolic stress and environmental stress.

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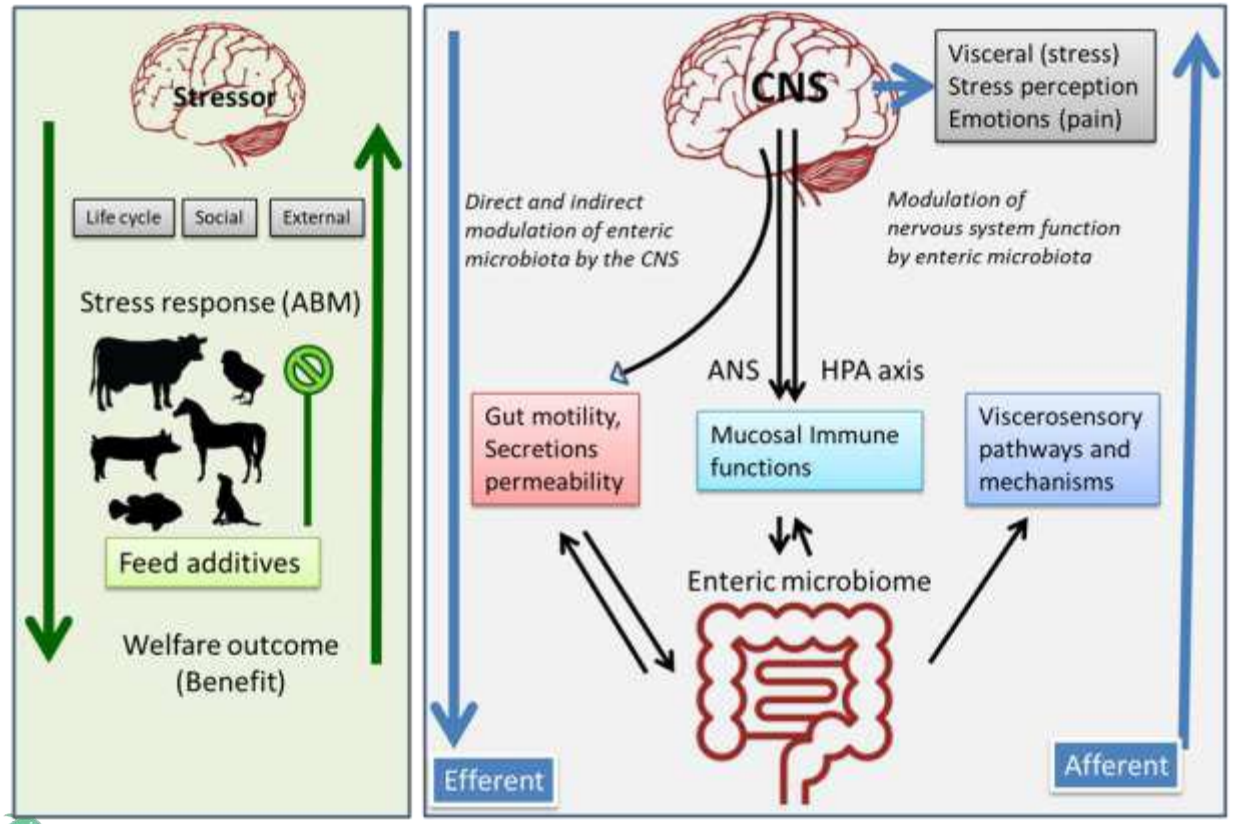
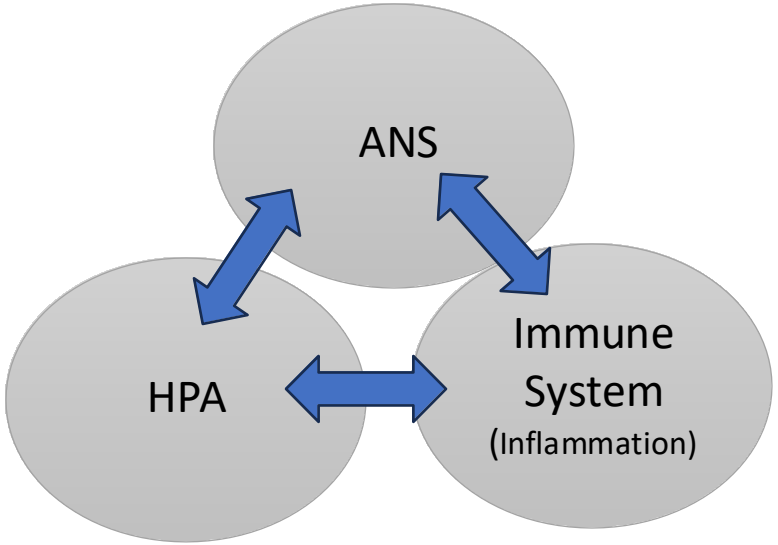
The physiological response to stress

Common neuro-endocrinological pathways and peripheral (detrimental) effects in all animal species



The Autonomic Nervous System (**ANS**) & the Hypothalamic-Pituitary-Adrenal (**HPA**) axis are interconnected systems mediating the body's response to stress.



These pathways are described in more detail in the technical report submitted earlier by FEFANA

Examples of stressors in animals with known detrimental outcomes

- *Pigs*
- *Poultry*
- *Ruminants*
- *Teleost fish*
- *Companion animals*

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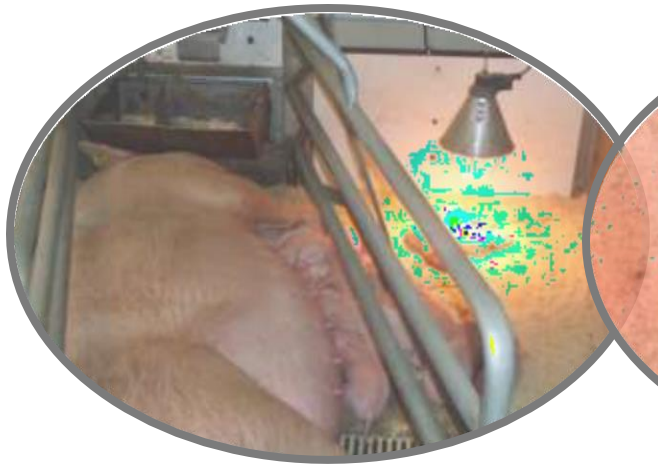
Pigs

Metabolic



Parturition:
Metabolic stress syndrome sow
Hypoxia/hypoglycaemia in piglet

Metabolic

Gut development
and establishment
of the microbiome.
Innate and adaptive
Immunity

Metabolic & Social

Weaning:
Dietary changes and
regrouping

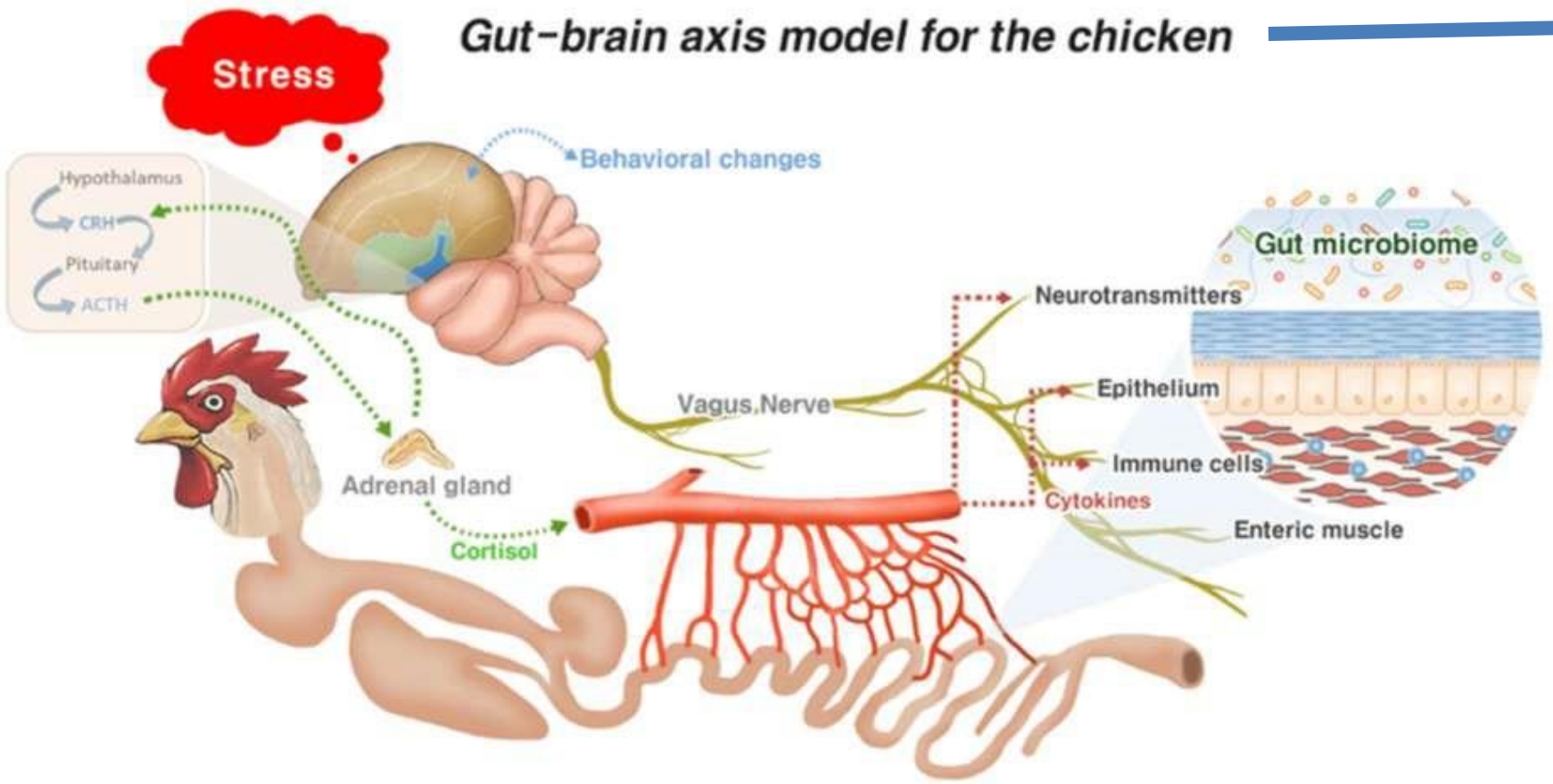
Social, Metabolic & Environmental

Social stress:
Crowding, dullness
Metabolic: feeding
Environmental: heat stress

Dysbacteriosis - systemic inflammation (immuno-suppression) – aggressive behavioural

Poultry

Metabolic, social and environmental stressors



Gut health:
Dysbacteriosis & Leaky gut

Immuno-modulation
Increase susceptibility to infections (incl. Salmonellosis)

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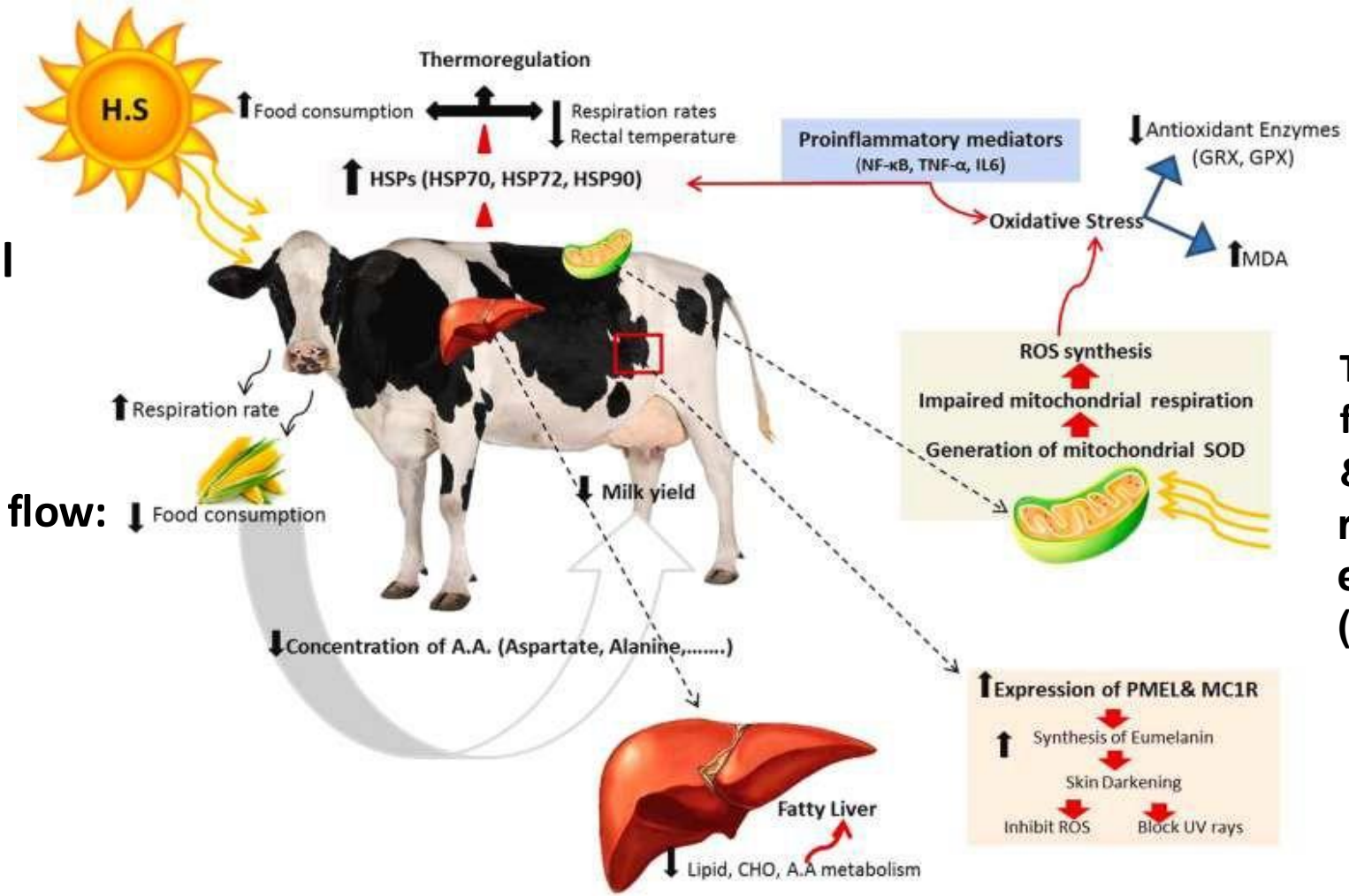
https://doi.org/10.3390/vaccines10020172

Ruminants (cattle)

Environmental
Heat stress

Repartition of blood flow:
Organ hypoxia



Tissue Hypoxia and ROS formation
&
related physiological endpoints (biomarkers)

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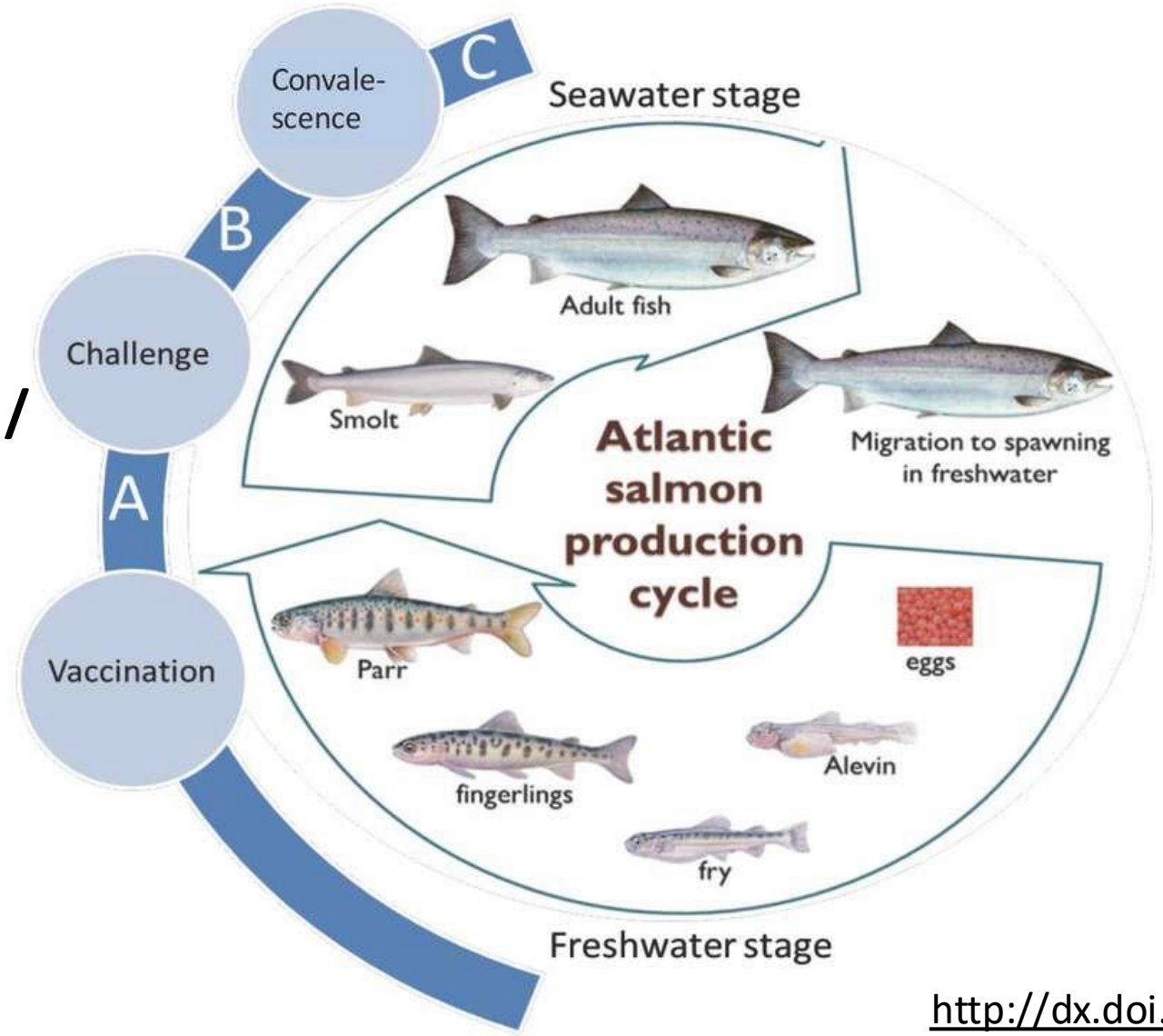
https://doi.org/10.1016/j.jtherbio.2018.12.013

Teleost Fish - Atlantic Salmon

Inherent Stressor / Challenges:
<u>Smolting</u>



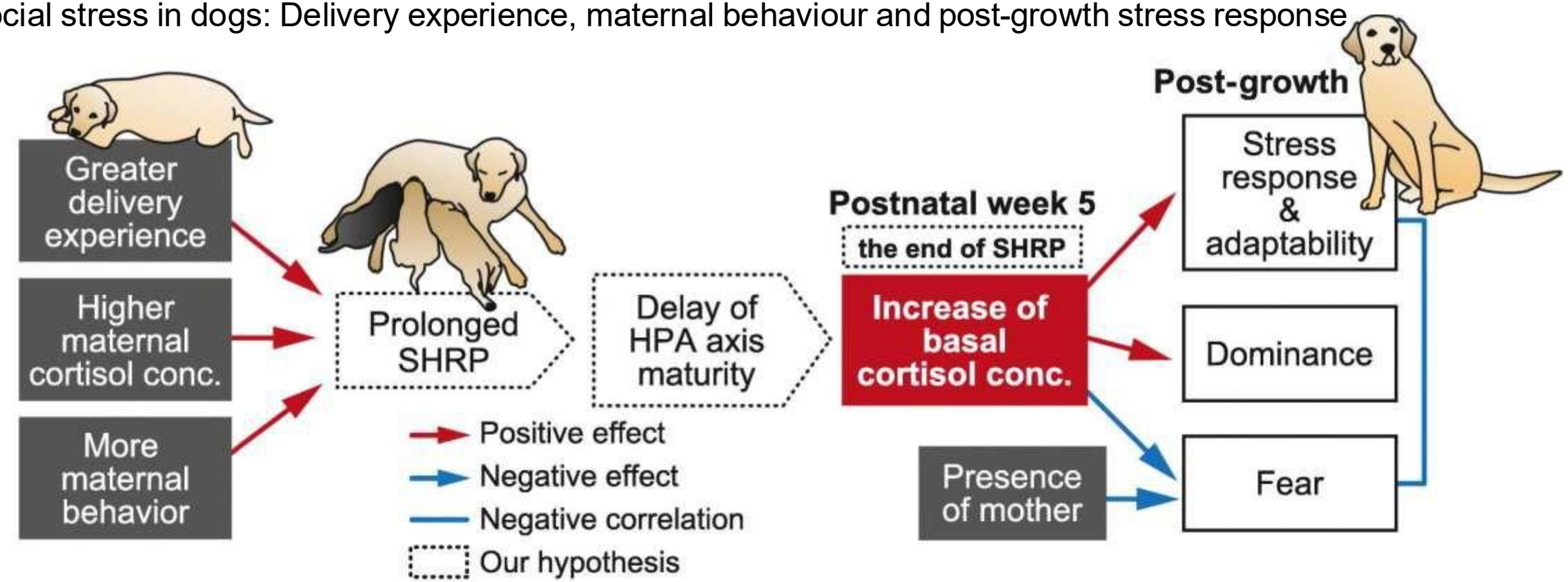
Immunosuppression:

Increase susceptibility to infectious microbial and parasitic diseases
Behavioural changes

http://dx.doi.org/10.1371/journal.pone.0148467

Companion Animals

Social stress in dogs: Delivery experience, maternal behaviour and post-growth stress response



More quantities of maternal variables prolong the stress hyporesponsive period (SHRP).

High cortisol concentrations at postnatal week 5 are linked to resilience post-growth.

https://doi.org/10.1016/j.yhbeh.2021.105055

FEFANA Technical Report overall Conclusions

The physiological stress response is a well-defined cascade of adaptive mechanisms, characterized by:

- High consistency in the measurable physiological alterations at the organ or tissue level
- Some variability in intensity dependent on the nature of the stressor
- Quantifiable by clinical observations (behaviour – neurological signs) and various physiological and immunological endpoints.

FEFANA considerations as regards technical requirements for demonstration of efficacy of PCS (1)

Considering that examples and models of physiological stress conditions have been published for almost all animal species, and that biomarkers of biochemical and behavioural changes have been published, it is recommended that

- **the selected experimental model should allow a dose-response evaluation.**

Appropriate **endpoints may include:**

- feed and water consumption
- behavioural changes
- *in vivo* and/or *ex vivo* test parameters: e.g. endocrinological, immunological, and organ- and cell-specific physiological alterations involved in the specific stress response

Examples can be found in the technical report submitted earlier by FEFANA

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FEFANA considerations as regards technical requirements for demonstration of efficacy of PCS (2)

PCS are generally fed to help animals cope with stress situations that can occur for a defined period of their life cycle (e.g. heat stress)

- **Efficacy testing should focus on short term experiments**, by applying a well-defined stress model (as described in the literature) or in field trials with typical stress scenarios. Depending on the stress model, observational (clinical) endpoints and quantifiable endpoints (biomarkers) need to be defined *a priori* and reported (treated vs non-treated animals).
- In **exceptional cases**, long-term testing may be relevant

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FEFANA considerations as regards technical requirements for demonstration of efficacy of PCS (3)

Optional cluster approach

Considering that the stress response and species-specific biomarkers are very similar in all **age groups** and often across (physiologically) **related species**, extrapolation of finding across species is possible.

This can be applied for example to:

- Metabolic stress associated with (nutritionally necessary) feed changes in piglets, weaners and growing Suidae
- Metabolic and environmental stress in chickens to be extrapolated to layers for rearing and/or other poultry species
- Heat stress in cattle and other ruminants

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Summary of the tiered approach in the development of PCS

Pre-application phase (R & D)*

Selection of bioactives based on target identification, Stress-induced physiological Changes based on literature and in vitro data

Toxicological clearance including respective applications see EFSA, 2024

Demonstration of efficacy: short term studies

In vivo **proof of concept** in a defined **short term model experiment** (challenge model) in the target animal species, including dose range finding & selection of quantifiable endpoints (biomarkers of effect)

Technical clearance (feed / water applications) See EFSA, 2024

Extrapolation to other age categories and animal species

Cluster approach:
Verification of indication (in silica)
Validity of biomarkers (in silico)
Extrapolation of dosing regimens

Confirmatory *in vivo* study in every target animal species

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* please note that many products/ ingredient candidates have been licensed already for other functional groups as a feed additive)

THANK YOU!