ENDOCRINE SOCIETY
Hormone Science to Health

November 23, 2026

Submitted electronically via Regulations.gov to docket FDA-2025-N-3262-0001

Re: Substances Generally Recognized as Safe; Proposed Rule

The Endocrine Society appreciates the opportunity to comment on the Food and Drug Administration's (FDA's) proposed rule, "Substances Generally Recognized as Safe." The Society is the world's oldest, largest, and most active professional organization devoted to research on hormones and the clinical practice of endocrinology. Our membership includes more than 18,000 scientists, physicians, educators, nurses, and students in more than 100 countries, including leading experts on endocrine-disrupting chemicals (EDCs) and their effects on human health across the life course.

Our members agree that mandatory notification of GRAS status would improve FDA's visibility into substances added directly and indirectly to food. However, the proposal as written fails to correct critical gaps that are particularly relevant for chemicals capable of interfering with hormone biology. The proposal also establishes new policies that would maintain exposure to EDCs at biologically relevant levels that could cause harm. **Because of these deficiencies, we urge FDA to withdraw the proposed rule and reconsider its approach.** We assert that any proposed rule must ensure that the GRAS pathway cannot be used where the available evidence is insufficient to establish safety using contemporary, independent science. We offer several recommendations below that, in our view, are necessary to bring a proposed rule on GRAS into better alignment with the latest endocrine science.

Mandatory notification is a useful first step, but it is not a substitute for pre- or postmarket safety review

FDA correctly recognizes that the voluntary system has prevented the Agency and the public from obtaining a complete picture of substances used in food. Mandatory notification is an important step towards gathering necessary information; however, the proposal as written would continue to allow purported GRAS substances to be marketed without FDA premarket review. Furthermore, there are no penalties for noncompliance in and of itself, and a failure to notify would only be considered as a factor in prioritizing postmarket review, with uncertain timeframes involved given limited Agency resources.

FDA should require submission before a substance enters commerce and should make clear, by issuing an "insufficient basis letter, that an incomplete or unsupported notice does not satisfy the notification requirement. Issuing such a letter would prevent the company from marketing its product as GRAS. FDA should establish a defined review period and should not permit marketing under a GRAS claim until the Agency has determined that the notice

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is complete. Where the evidence does not support a GRAS conclusion, the substance should not be allowed in food until a detailed safety assessment has been completed, including for endocrine activity. FDA should clarify its enforcement approach and establish a mechanism to suspend or reject reliance on GRAS where required information is missing or where emerging scientific evidence raises a safety concern.

The GRAS framework must explicitly address endocrine-disrupting chemicals (EDCs)

An EDC is an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action. Endocrine effects may occur at biologically relevant exposures, may follow non-monotonic dose-response relationships, and may depend strongly on the timing of exposure. Conventional toxicology approaches focused on overt toxicity at high doses often fail to recognize biologically meaningful endocrine endpoints. While the proposed rule rightly exempts carcinogens, we are disappointed that the same exemption does not apply to EDCs, which the Agency's own 2014 guidance noted are a risk. A GRAS conclusion cannot be scientifically justified as health protective if the evidence supplied fails to interrogate the endpoints and exposure windows most relevant to the substance's potential hazards.

FDA should specify that a substance with evidence of endocrine activity, or without adequate information to evaluate endocrine activity, is not eligible for a GRAS conclusion based solely on conventional toxicology data. At a minimum, notices should include a structured evaluation of endocrine-related evidence, including low-dose effects and the possibility of non-monotonic dose responses.

FDA should not expand the TOR exemption to direct food additives

FDA proposes to revise 21 C.F.R. § 170.39 and extend the Threshold of Regulation (TOR) exemption framework beyond food-contact substances to substances used directly or indirectly in food with an estimated daily intake of 0.025 micrograms per kilogram body weight per day. A generic exposure threshold is not an adequate basis for concluding that endocrine risk is negligible. The Society has long cautioned that it cannot be assumed that a safe threshold exists for EDCs. Hormones operate at extremely low, biologically relevant concentrations; exposure to chemicals with endocrine activity at similar environmental levels may therefore be hazardous. Furthermore, susceptibility varies by developmental stage (e.g., infancy, pregnancy, puberty) and health status, and non-monotonic responses can make relatively high-dose observations unreliable predictors of low-dose safety.

FDA should withdraw the proposed expansion of TOR and FDA should categorically exclude substances that are known or suspected EDCs, i.e., substances with endocrine activity in screening or mechanistic studies, from GRAS consideration. Additionally, the proposal should be much more specific about how estimated daily intake will be calculated

and verified. A safety determination cannot rest on exposure estimates limited to a single food or a notifier-selected use when the same substance may occur across many foods, food-contact materials, processing aids, flavors, contaminants, or other sources.

FDA must account for cumulative and mixture effects

People are exposed to mixtures, not one chemical at a time. Multiple direct and indirect additives may each fall below a numerical threshold yet act on the same hormone pathway, organ system, or to elicit an adverse outcome. Evaluating each substance and each use in isolation can therefore underestimate risk.

FDA should require cumulative assessment for substances that share mechanisms, biological pathways, target organs, or adverse outcomes. The assessment should include structurally related substances and reasonably foreseeable co-exposures from direct additives, food-contact materials, and other dietary sources. FDA should not grant a TOR exemption where identity or use information is insufficient to conduct this assessment. A notifier's assertion that one intended use is below a threshold should not substitute for an analysis of aggregate exposure and combined effects.

Safety information must be transparent and capable of independent validation

The proposal presents mandatory notification as a transparency reform, but that objective is undermined if data necessary to support safety is not available to the public for independent validation. Proposed § 170.250(e) would ask a notifier to explain how a GRAS conclusion can rest on non-public safety-related information identified as exempt from disclosure. That approach does not resolve the basic scientific problem i.e., that the public, including independent academic scientists generating new information on endocrine hazards, cannot evaluate safety or incorporate data into their analyses based on evidence they cannot access. Independent analysis is particularly necessary if a GRAS conclusion is supported by a panel composed of individuals from regulated entities.

FDA should require public disclosure of the safety studies, exposure analyses, methods, conflicts of interest, expert-panel composition, and reasoning necessary to support a GRAS conclusion, with narrow protection only for information that is genuinely confidential and not material to safety. The final rule should state that non-public evidence cannot supply an essential element of the basis for GRAS affirmation.

Existing substances require a substantive review

We are concerned that the proposal, as written, continues to allow GRAS substances already on the market to continue to be used without safety substantiation. FDA should require complete notices for existing substances on a defined schedule and should prioritize review based on hazard, exposure, data gaps, and susceptibility. Because of the myriad GRAS

chemicals assumed to be on the market currently, postmarket review is essential for correcting legacy determinations and must be considered complementary to adequate premarket review.

Conclusion

The Endocrine Society supports requiring GRAS notification, but FDA must do more than create a registry of industry conclusions for new substances. A scientifically credible framework would recognize that endocrine hazards may occur at low exposures, during sensitive windows, through non-monotonic responses, and in combination with other chemicals. It must also ensure that exposure estimates cover the whole diet with safety data that is publicly reviewable, and where failure to comply has meaningful consequences.

We urge FDA to withdraw the current proposal and substantially revise a future rule to:

- exclude EDCs and inadequately tested substances from GRAS eligibility,
- withdraw the expansion of TOR to direct food additives,
- require aggregate and cumulative assessment,
- explicitly protect susceptible populations,
- mandate public safety information,
- ensure that current GRAS chemicals are included in mandatory notifications,
- establish enforceable premarket notification and review requirements.

Thank you for considering our comments. The Society and our members stand ready to assist FDA in developing scientifically robust approaches to protect the public from EDC-related hazards.