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Public comments on the **Endocrine Disruptor Screening Program: Near-Term Strategies for Implementation**, Docket ID No. EPA-HQ-OPP-2023-0474.

Submitted via Regulations.gov:
https://www.regulations.gov/search?filter=EPA-HQ-OPP-2023-0474

We are writing from Silent Spring Institute to provide comments on EPA's strategies to implement the Endocrine Disruptor Screening Program (EDSP). Silent Spring Institute is a non-profit research organization that studies the links between environmental chemicals and disease, with a focus on breast cancer and other women's health issues. Breast cancer is a major public health burden as the most common cancer diagnosis among all individuals in the United States (US).[1, 2] In the past two decades, rates of BC in the US have significantly increased for females overall and for females under age 50,[1, 3, 4] with a 2.6% increase in women under 50 between 2016 to 2019.[4] Furthermore, among people in the US under age 50, breast cancer incidence is 6 times more common than any type of cancer in men, and rates of death from breast cancer are more than double that of any other cancer among women and men.[3] In the face of these staggering statistics, it is critical to prevent exposures that may increase BC risk.

Silent Spring is concerned that EPA's pesticide safety reviews have missed effects of chemicals that are likely to increase breast cancer risk and that current and past pesticide exposures may pose unacceptable risks to workers and the general population. We have published several relevant studies in peer-reviewed scientific journals that support this claim. We have shown that mammary gland tumors caused by pesticides are often inappropriately dismissed by EPA's Office of Pesticide Programs (OPP) despite the likelihood they will also increase breast cancer risk.[5, 6] We have highlighted limitations in guideline toxicology studies that cause OPP to miss the effects of pesticides on mammary gland development in ways likely to increase breast cancer risk.[7, 8] These effects can result from endocrine disruption. Using EPA's own data, we have also shown that pesticides and other chemicals cause cells to increase estradiol (E2) and progesterone (P4) steroidogenesis[9, 10] – a pathway highly relevant to breast cancer – and that this effect can help predict chemicals that cause mammary gland tumors.[6] We have shown that EPA's current endocrine screening and testing is incomplete and misses important breast cancer pathways, such as aromatase activation and progesterone receptor activity.[6, 8, 9] The attached table, Attachment2_BCrelevantPesticides_EDSPcomment.xlsx, lists 147 pesticide active ingredients that we have identified as having the potential to increase breast cancer risk, including 30 that cause mammary gland tumors in rodents, 78 that increase E2 synthesis, 63 that increase P4 synthesis, and 33 that activate the estrogen receptor (ER). Thus, EPA's past and proposed actions to address endocrine effects of pesticides, including under the EDSP, are insufficient to protect women's health.

Here we provide comments on EPA's proposed actions described in **Endocrine Disruptor Screening Program: Near-Term Strategies for Implementation (**Docket ID No. EPA-HQ-OPP-2023-0474**).** We commend EPA OPP for taking steps to fulfill its mandate to test pesticides for harm via endocrine disrupting modes of action. We appreciate the opportunity to comment on EPA's proposed prioritization of pesticides for evaluation and the current evidence under consideration. Our comments directly address the other scientifically relevant information (OSRI) requested for the Group 1 and Group 2 prioritized pesticides that lack an *in vivo* reproductive/developmental toxicity study. We also provide recommendations to modify EPA's proposed framework for prioritizing pesticides for evaluation of

estrogenic/androgenic effects (Figure 1 in List of Conventional Registration Review Chemicals for Which an FFDCA Section 408(p)(6) Determination is Needed) to better protect human health.

EPA's plan to prioritize gathering new information about the ability of pesticides to cause harm by endocrine pathways does not address known weaknesses that are likely to lead to missing effects of concern

EPA's framework outlined in the document "List of Conventional Registration Review Chemicals for Which an FFDCA Section 408(p)(6) Determination is Needed **is biased towards identifying false positive results and doesn't address the potential for false negatives or prioritize filling data gaps, which can lead to EPA missing important health effects of pesticides.** This bias is evident in how EPA has prioritized assessment of the 317 conventional pesticides that have not been tested in an updated reproductive toxicity guideline study. We provide OSRI for these pesticides below, but first we provide comments about EPA's overall framework.

The pesticides EPA has classified as "Group 1" cases – without reproductive toxicity studies but showing positive ER/androgen receptor (AR) pathway scores – should be tested as soon as possible in updated studies to identify potential effects on reproduction and development. Until those data are available, EPA should consider adding an additional uncertainty factor to the risk evaluations for those pesticides and updating restrictions on use and tolerances to reflect this uncertainty.

In addition, we want to emphasize that even the so-called "updated" reproductive toxicity studies are limited in their ability to detect effects on endocrine disruption. For example, the two-generation reproductive toxicity study guideline updated in 1998 (OCSPP 870.3800,[11] performed on 82 of the 86 pesticides with an *in vivo* reproductive study) does not require any assessment of the mammary gland, and the extended one-generation reproductive toxicity study (EOGRTS; OECD TG 443)[12] guideline does not require sufficient evaluation of the mammary gland.[8] Endocrine disruptors can adversely affect mammary gland biology at lower doses than those that affect other guideline endpoints, such as the uterus, ovaries, and reproductive parameters.[7, 13-18] We are especially concerned that some of these mammary gland effects will lead to increased risk of breast cancer, impairment of lactation, and altered development during embryonic, pubertal, pregnancy, and reproductive senescence phases.[7, 8] These effects have been demonstrated in rodents for atrazine, organochlorine pesticides, bisphenols, per- and polyfluoro alkyl substances.[8] These gaps in assessment for breast-related effects are critical to fill in order to protect public health.

As a result of these weaknesses in the "updated" reproductive and development study designs, we are concerned that relevant effects may have been missed for the 86 pesticides that have been tested and that EPA considers to have sufficient evidence for estrogenic and androgenic effects. For example, among those pesticides, we have identified 7 as potential breast carcinogens based on rodent mammary tumors or relevant EDC activity (see attached table). Testing for effects on the mammary gland should be required for these, and additional uncertainty factors introduced in the interim to protect against potential effects.

The pesticides EPA has classified as "Group 2" cases – without reproductive toxicity studies or ER/AR pathway scores – should also be a top priority. These chemicals have the least data for endocrine disrupting potential and therefore most urgently require assessment. In addition to producing ER/AR pathway model data, EPA should use existing ToxCast data and other publicly available data for other endocrine-related effects (e.g., H295R screening for steroidogenesis, discussed further below) in considering these chemicals' endocrine disrupting potential. Database uncertainty factors should be considered for these pesticides as well, until assessment is complete.

In addition to not prioritizing filling data gaps, OPP's implementation of the EDSP is also vulnerable to missing important effects of endocrine disruptors because of EPA's focus on estrogen, androgen, and thyroid (E, A, and T) activities. Thus, EPA is expected to – and seems to accept that it will – miss effects from disruption of other hormonal pathways. Additional investment in understanding endpoints of endocrine disruption and modifying reproductive and developmental testing to detect them will benefit public health. In addition, ER/AR pathway models miss modes of hormone disruption other than interaction with receptors highlighted as key characteristics of EDCs.[19] For example, they don't detect chemicals that alter steroidogenesis. Finally, *in vitro* assays used for screening can lead to false negatives because they are limited in their ability to predict effects at the organismal level, such as through inter-organ signaling and tissue-specific processes (e.g., hypothalamus-pituitary-gonadal axis, hormone metabolism in peripheral tissues, epigenetic alterations). Thus, EPA's choice to rely on the estrogen and androgen (ER and AR) pathway models to flag endocrine disruptors misses many key aspects of endocrine disruption.

We are also concerned that the federal register docket (ID No. EPA-HQ-OPP-2023-0474) states, for the "Group 3" pesticides that tested negative in the ER/AR pathway models, that "current data suggest no potential for estrogen or androgen activity." In fact, chemicals that test negative in these models should not be considered to have evidence for lacking estrogen or androgen activity. For example, chloro-s-triazines, malathion, ametryn, dimethomorph, cyfluthrin, and other pesticides are not active at the ER but they do increase E2 synthesis,[6] so EPA must consider these effects. As many have noted, including the EPA's Children's Health Protection Advisory Committee, New Approach Methodologies (NAMs, such as the ER/AR pathway models) "should be used for screening purposes and to indicate a hazard or upgrade concern for a hazard, but **conclusions about the absence of hazard cannot be drawn solely based on NAMs data**"[20] (emphasis ours). Therefore, Group 3 pesticides should be investigated for other possible modes of estrogen or androgen disruption, as well as other endocrine effects as we explain above.

EPA should incorporate its own data for other modes of endocrine disruption, such as steroidogenesis, in EDSP evaluations

We are concerned that EPA is not using its own high quality data on steroidogenesis[9, 10, 21] as part of its assessment on endocrine disruption for the 317 conventional pesticides that lack an *in vivo* reproductive toxicity study (Figure 1 of List of Conventional Registration Review Chemicals for Which an FFDCA Section 408(p)(6) Determination is Needed). We have recently shown that steroidogenesis of E2 and P4 is an important mode of endocrine disruption overrepresented (enriched) among chemicals that induce mammary tumors in rodents, and in fact, E2 and P4 steroidogenesis is more significantly enriched among rodent mammary carcinogens than ER agonism.[6] Given how important these pathways are in breast cancer, these findings indicate that steroidogenesis should be emphasized in chemical hazard assessments.

We are providing OSRI from EPA's H295R steroidogenesis screening published by Haggard et al[10] (concentration-response [CR] format) and Karmaus et al.[21] (single dose format) that measures 11 hormones including estrogens, androgens, progestogens, and corticosteroids for the conventional pesticides prioritized in this framework, none of which EPA has considered in their assessments. Specifically, we summarize results for E2 and P4 steroidogenesis, and EPA can refer to its publications for information about other hormones. The attached table includes data for hazard identification including E2 and P4 steroidogenesis, mammary carcinogenicity, ER pathway model scores, and genotoxicity for pesticides with active registrations in EPA's Pesticide Product Information System. These data were recently published in Kay et al. 2024[6].

We highlight results for pesticides in EPA's prioritization framework here, noting that EPA has not considered these data in its EDSP assessment:

- **Group 2 (not tested in ER/AR pathway models):** EPA has tested three Group 2 cases (methiocarb, prothioconazole, and rimsulfuron) in the H295R-CR steroidogenesis assay.[10] The results show that methiocarb increases both E2 and P4 production, and prothioconazole and rimsulfuron also increase P4 production.[9, 10]
- **Group 3 (negative in ER/AR pathway models):** EPA has tested at least 27 chemicals in this list in the H295R assay in either CR or single-dose formats, and 21 showed significant activity in those assays. Of the chemicals tested in CR, 13 (1-methyl-3-phenyl-5-(3-(trifluoromethyl)phenyl)-4-pyridone, 2,4-dimethylphenol, ametryn, bromacil, chlorpropham, coumaphos, ethyl 1-naphthaleneacetate, fluazifop-P-butyl, formetanate HCl, lactofen, phenothrin, prometon, and simazine) induced production of E2, and 11 (2,4-dimethylphenol, ametryn, benfluralin, butralin, coumaphos, fluazifop-P-butyl, flumiclorac-pentyl, formetanate HCl, lactofen, prometon, and simazine) induced production of P4.[9, 10] Of the chemicals tested only in the single dose, three (benzyl benzoate, m-cresol, and phorate) increased E2 production and dichlorvos induced P4 production.[21] We note that other Group 3 chemicals may have been tested in H295R as well, but without unique standard identifiers such as CAS numbers in the documents provided in this docket, we may have missed some while cross-referencing the Group 3 list with H295R data.
- **Group 1 (positive in ER/AR pathway models):** Sixteen Group 1 pesticides have been tested in the H295R assay. Of the chemicals tested in the CR format, five (acibenzolar-s-methyl, clomazone, dimethomorph, fenitrothion, and prallethrin) induced E2 production and ten (chlorfenapyr, clomazone, dimethomorph, fenbuconazole, fenhexamid, fenitrothion, flumetralin, napropamide, prallethrin, and N-(3,4-dichlorophenyl)propanamide) induced P4 production.[9, 10] In addition, bensulide induced P4 production in the single-dose format of H295R but was not tested in CR.[21]
- Of the **86 pesticides with updated *in vivo* reproductive toxicity studies submitted to EPA**, for which EPA considers no additional evidence for estrogenic or androgenic activity to be necessary, testing in H295R-CR shows that difenoconazole, etridiazole, pacloburazol, and triticonazole induce E2 production and etridiazole, MCPA, and triflumizole induce P4 production. As we discussed above, these effects may not be evident from the study design and data collected in the EPA two-generation (OCSPP 870.3800)[11] and OECD extended one-generation (EOGRTS; TG 443)[12] reproductive toxicity assays. For example, mammary gland assessment is not included in EPA's "updated" two-generation reproductive toxicity assay, and it is optional in the EOGRTS. E2/P4 steroidogens may affect the breast without producing obvious changes in tissues collected in EDSP Tier 2 *in vivo* reproductive toxicity assays,[7, 13-18] such as through local activation of aromatase in mammary adipose tissue. EPA should incorporate this evidence for steroidogenesis into weight of evidence evaluations of endocrine disruption for these 86 pesticides and should include mammary gland assessment in required reproductive and developmental studies.

We are also concerned that the weight of evidence evaluations for List 1 pesticides that have undergone EDSP Tier 1 Screening (Status of Endocrine Disruptor Screening Program (EDSP) List 1 Screening Conclusions) only consider sponsor-submitted test data for steroidogenesis of E2 and testosterone, ignoring EPA's own high throughput H295R steroidogenesis screening data as published in Haggard 2018[10] and Karmaus 2016.[21] List 1 pesticides are included in the attached table with the summary of H295R screening for PPIS-registered active pesticide ingredients.

Notably, the steroidogenesis data we summarized above only relate to increases in E2 and P4 synthesis, but the H295R ToxCast assay also measures estrone, three androgens (testosterone, dehydroepiandrosterone, and androstenedione), and three additional progestogens (pregnenolone, 17alpha-hydroxypregnenolone, and 17alpha-hydroxyprogesterone). EPA should use these measurements as further evidence for endocrine disruption in EDSP, particularly since these data inform estrogen and

androgen effects not reflected in the ER and AR pathway models. Although EDSP has a stated focus on E, A, and T pathways, data are available for other important hormones like progestogens, and these should not be discounted due to an outdated exclusive focus on E, A, and T pathways.

We emphasize the value of the H295R assay format that measures production of 11 hormones because it is more informative of chemical effects on steroidogenesis than the EDSP Tier 1 H295R assay that only measured E2 and testosterone. We are concerned that EPA's recent publication of a new H295R assay that utilizes fluorescence to measure E2 and testosterone production[22] suggests the agency plans to move away from measuring the additional hormones that made the data from Karmaus et al 2016[21] and Haggard et al 2018[10] so valuable. We encourage EPA to adopt the 11-hormone H295R screen into the EDSP in place of the outdated OCSPP Guideline 890.1550 and require sponsors to provide new data from that assay format. At a minimum, P4 should be included because of its important role in breast development and carcinogenesis.[23, 24]

We also emphasize that EPA should rely on concentration-response data from the H295R assay using the data analysis and statistical method described in Haggard et al 2018[10] to identify significant responses and not rely on output from the EPA Chemical Dashboard tcpl automated data processing pipeline. The Haggard approach considers not just the concentration-response effects for each hormone measured, but also overall disturbance of the hormone metabolic pathway by integrating all hormone effects into an adjusted maximal mean Mahalanobis distance. The tcpl automated data-processing pipeline produces false negatives.[9] For example, Haggard et al., 2018 shows that cyfluthrin significantly increased production of E2, estrone, corticosteroids, and to a lesser extent androgens, demonstrating interference at multiple steps along the steroidogenic pathway.[10] Cyfluthrin was one of the strongest E2-inducers tested in that study (Figure 1).

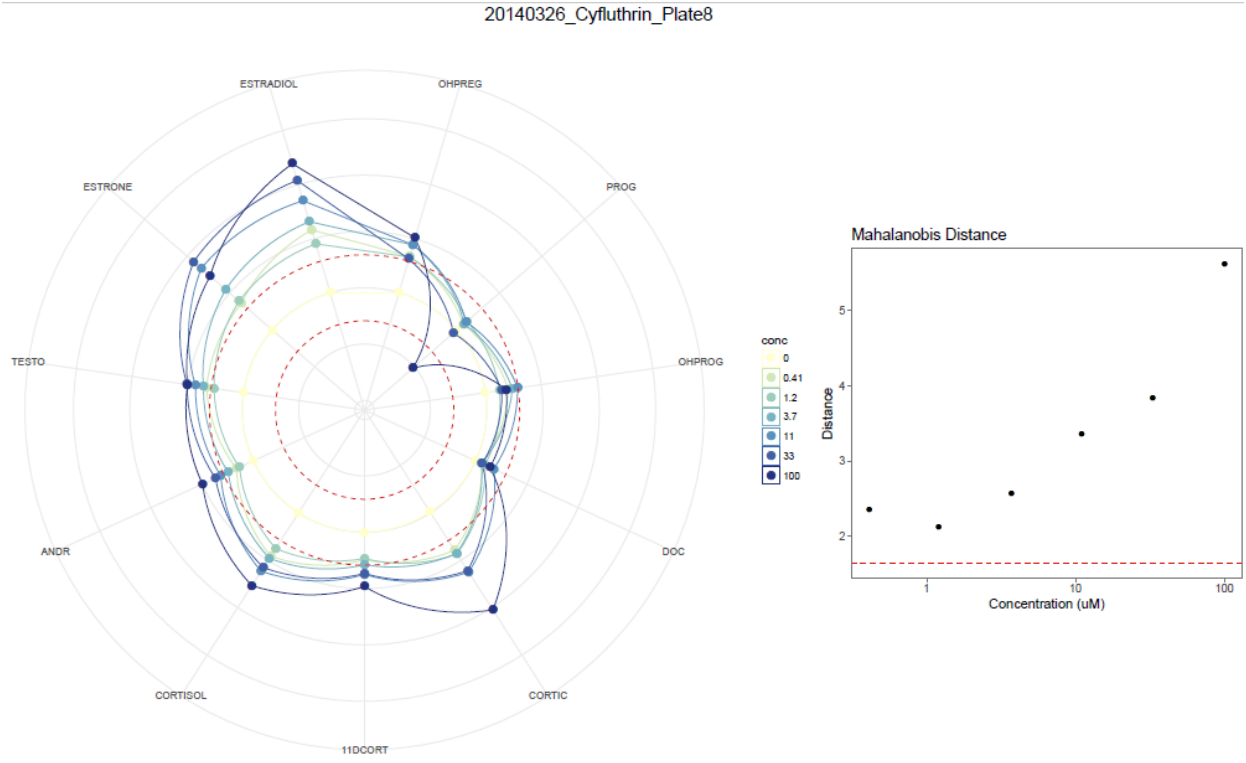

Figure 1: Radar plot and Mahalanobis distances of cyfluthrin H295R concentration-response testing (Haggard et al. 2018, Supplemental material file 9). E2 is shown at the top left of the radar plot, demonstrating a robust concentration-dependent increase in E2 production that is significant at all doses (indicated by dotted red line).

Despite these data from Haggard 2018 that show a clear effect of cyfluthrin increasing E2, tcpl analysis shown on the CompTox Dashboard classifies cyfluthrin as inactive for E2 steroidogenesis based on a different analysis of the same underlying data (Figure 2). This may reflect tcpl not using control wells (no chemical added) as a reference comparison, and instead setting effects at the lowest concentration as the reference level. In addition, based on the tcpl concentration-response plot below, it appears that tcpl set the control as the higher E2 level measured out of two replicates of the lowest concentration, rather than the average. As documented in Haggard 2018, cyfluthrin significantly increased E2 production at all doses tested (Figure 1), but this potent effect is masked when the lowest cyfluthrin concentration is used as the control (Figure 2). EPA's choice to use the low concentration wells as controls for tcpl data processing in ToxCast is liable to cause the agency to miss important effects, as it did in this case. As we have reported previously, only 25% (46) of the 182 chemicals that increased E2 levels using Haggard's data analysis were considered active using tcpl.[9]

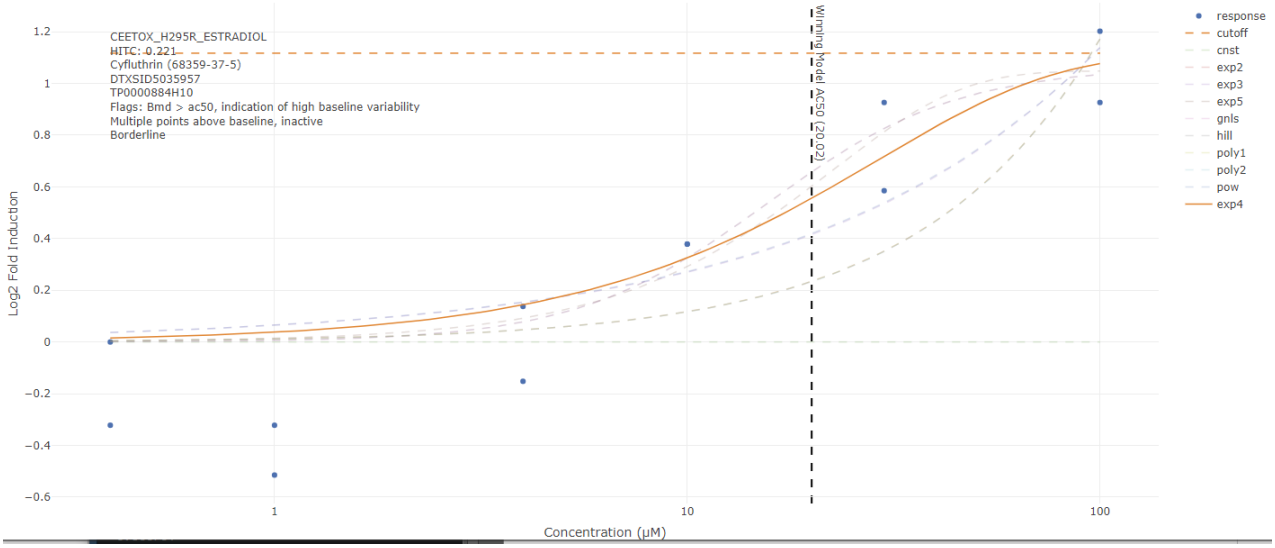

Figure 2: Screenshot of CompTox Dashboard tcpl analysis of cyfluthrin effect on E2 steroidogenesis. Note EPA's conclusion that cyfluthrin is inactive. Note that the true control well (no chemical added) data are not shown. The reference or "zero" is set at the highest E2 level measured out of two replicates at the lowest concentration of cyfluthrin.

EPA should validate *in vivo* EDSP studies for detecting steroidogens

Finally, we are concerned that chemicals that increase E2 steroidogenesis may not be detected in EDSP Tier 1 or Tier 2 assays. We demonstrated that rodent mammary carcinogens are enriched for *in vitro* E2 (and P4) steroidogenic activity,[6] and we are aware of at least one study showing that a potent E2-steroidogen that is not active in the ER pathway model, 2,4-dichlorophenol, significantly altered mammary gland morphology in a guideline reproductive/developmental toxicity study at doses below those where uterine weights were increased and implantation sites and live births were reduced.[13] This study demonstrates the importance of assessing steroidogenesis as a significant mode of endocrine disruption and assessing the mammary gland as a sensitive endpoint in reproductive/developmental toxicity studies (which do not currently require mammary gland assessment).[8, 11, 12] However, we are not aware of efforts to investigate whether reproductive/developmental toxicity study endpoints can detect steroidogens. EPA should identify a steroidogenic positive control (e.g., an aromatase activator) and test what endpoints it affects in reproductive/developmental toxicity studies to make sure the *in vivo* studies include assessment of sensitive endpoints. This *in vivo* study should include mammary gland assessment

as well as standard guideline study endpoints, both because the mammary gland is more sensitive than other endpoints for certain endocrine disruptors[8] and because the mammary gland expresses aromatase,[25, 26] potentially altering local E2 levels and causing effects that are not evident in other organs. Validating reproductive/developmental toxicity studies to make sure they can detect steroidogens that do not interact with the ER or AR will support better decisions about testing, prioritization, and risk assessment going forward.

We hope these comments support EPA's efforts to fulfill its EDSP pesticide testing requirements to better protect public health. Meeting this goal will require re-prioritizating pesticides that require additional data for endocrine disruption, more comprehensive screening for endocrine effects, and improved *in vivo* study designs so that important effects are not missed.

Sincerely,

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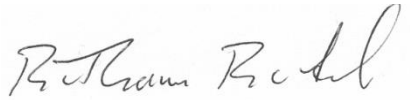

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