Docket Number EPA-HQ-OPP-2010-0127
www.regulations.gov

Hymexazol

Proposed Interim Registration Review Decision
Case Number 7016

September 2016

Approved by: _____
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Date: 9/22/16

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I. Introduction

This document is the Environmental Protection Agency's (EPA or the Agency) *Proposed Interim Registration Review Decision* for hymexazol (PC Code 129107, case 7016), and is being issued pursuant to 40 CFR sections 155.56 and 155.58. A registration review decision is the Agency's determination whether a pesticide meets, or does not meet, the standard for registration in the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The Agency may issue, when it determines it to be appropriate, an Interim Registration Review decision before completing a registration review. Among other things, the Interim Registration Review decision may require new risk mitigation measures, impose interim risk mitigation measures, identify data or information required to complete the review, and include schedules for submitting the required data, conducting the new risk assessment and completing the registration review. For further information on hymexazol, additional documents can be found in EPA's public docket (EPA-HQ-OPP-2010-0127) at www.regulations.gov.

FIFRA, as amended by the Food Quality Protection Act (FQPA) of 1996, mandated the continuous review of existing pesticides. All pesticides distributed or sold in the United States generally must be registered by the EPA based on scientific data showing that they will not cause unreasonable risks to human health or to the environment when used as directed on product labeling. The registration review program is intended to make sure that, as the ability to assess and reduce risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects. Changes in science, public policy, and pesticide use practices will occur over time. Through the registration review program, the Agency periodically re-evaluates pesticides to make sure that as these changes occur, products in the marketplace can continue to be used safely. Information on this program is provided as http://www2.epa.gov/pesticide-reevaluation. In 2006, the Agency implemented the registration review program pursuant to FIFRA section 3(g) and will review each registered pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration.

EPA is issuing a proposed interim registration review decision for hymexazol so that it can (1) move forward with aspects of the registration review that are complete and (2) implement interim risk mitigation. The Agency is currently working with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service (together, the Services) to develop methodologies for conducting national threatened and endangered (listed) species assessments for pesticides. Therefore, although EPA has not yet fully evaluated risks to listed species, the Agency will complete its endangered species assessment and any necessary consultation with the Services for hymexazol prior to completing the hymexazol registration review. Likewise, the Agency will complete endocrine screening for hymexazol, pursuant to the Federal Food, Drug, and Cosmetic Act (FFDCA) section 408(p), before completing registration review. Last, EPA will determine whether pollinator exposure and effects data are necessary to make a final registration review decision for hymexazol and issue a data call-in (DCI) to obtain any such data prior to completing the hymexazol registration review.

Hymexazol is a systemic fungicide with one registered use as a seed treatment for sugar beet seeds to protect against seed diseases such as *Aphanomyces* spp. and *Pythium* spp. Although hymexazol is registered for use on sugar beet seeds, the Agency has determined that this use will

not result in any residues in food and can be treated as non-food use. There are no residential uses. Hymexazol was first registered in 1997, and therefore was not subject to reregistration.

The following list highlights significant events of the registration review of hymexazol. These documents and additional information on hymexazol can be found in EPA's public docket, EPA-HQ-OPP-2010-0127, accessed at www.regulations.gov.

- March 31, 2010 – Publication of the *Hymexazol Summary Document* for a 60-day public comment period. The Summary Document included the Preliminary Work Plan (PWP) and was accompanied by the Scoping Document and Problem Formulation.

- September 9, 2010 – Completion of the *Final Work Plan* (FWP) for hymexazol. One public comment was received during the 60-day comment period for the hymexazol PWP. The comment was submitted by the Center for Biological Diversity (CBD) but did not change the data and risk assessment needs or the timeline for the hymexazol registration review, so the FWP did not modify the PWP.

- October 7, 2011 – Generic Data Call-In (GDCI) for hymexazol issued. Data required through the hymexazol registration review GDCI include:
    - GLN 850.2100: Avian acute oral toxicity test
    - GLN 850.2300: Avian reproduction test
    - GLN 850.5400: Algal toxicity, Tiers I and II
    - GLN 870.3250: 90-day dermal toxicity
    - GLN 870.6200: Neurotoxicity screening battery
    - GLN 870.7800: Immunotoxicity

- January 6, 2016 – Publication of the *Hymexazol: Ecological Risk Assessment for Registration Review* and the *Hymexazol: Human Health Draft Risk Assessment in Support of Registration Review* for a 60-day public comment period. One comment was received from the Center for Biological Diversity (CBD), which is summarized below along with the Agency's response. The comment did not change the risk assessment methodology or results.

    COMMENTS RECEIVED FROM CBD (EPA-HQ-OPP-2010-0127-0017)

    Comment: The CBD comments focus on the EPA's duty to consult with the Services on the registration review of hymexazol in accordance with the Endangered Species Act (ESA). The CBD comments mention various aspects of the risk assessment process, including use of the best available data to develop listed species risk assessments, and evaluation of effects on listed species and their designated critical habitat. CBD also expresses concern regarding the rigor of the Agency's preliminary determinations regarding the effects of hymexazol on listed species and their designated critical habitat for the hymexazol registration review. In addition, CBD raises concerns surrounding the risk assessment methods employed by the Agency and the Agency's abilities to effectively balance risks and benefits of pesticides under FIFRA.

EPA Response: EPA has reviewed the comments from CBD and plans to address many of the concerns raised by CBD as part of the implementation plan for assessing the risks of pesticides to listed species based on the recommendations of the April 2013 National Academy of Sciences (NAS) report. EPA will address CBD's concerns specific to hymexazol in connection with the development of its final registration review decision for this pesticide.

- September 2016 – The Agency is now publishing the *Hymexazol Proposed Interim Registration Review Decision* in the public docket EPA-HQ-OPP-2010-0127 for a 60-day public comment period.

Additional information on hymexazol, including all public comments, can be found in EPA's public docket, EPA-HQ-OPP-2010-0127, accessed at www.regulations.gov.

II. Use and Usage

Hymexazol is a fungicide registered only for use as a commercial seed treatment for sugar beet, it has no other agricultural uses and no residential uses. It is used (15-25% of the sugar beet crop is planted with hymexazol treated seed) to control *Aphanomyces* spp. and *Pythium* spp. fungi. On an annual basis, it is estimated that 3,000 pounds of hymexazol is used to treat sugar beet seeds (*Hymexazol (129107) Screening Level Usage Analysis, 2014*). Sugar beets are predominantly cultivated in California, Colorado, Michigan, Montana, Minnesota, Nebraska, North Dakota, Oregon and Washington. For more information on the use and usage of hymexazol see *Appendix A for Hymexazol* published on November, 17, 2009; the *Hymexazol Screening Level Usage Analysis (SLUA)* published on June 9, 2014; and *Hymexazol Benefits Information (PC # 129107*), published on September 1, 2016 in the public docket EPA-HQ-OPP-2010-0127, at www.regulations.gov.

III. Scientific Assessments

A. Human Health Assessment

A summary of the Agency's registration review human health risk assessment is presented below. The Agency used the Health Effects Division (HED) scoping document, its supporting documents, and the most updated Agency science policies and risk assessment methodologies to prepare a quantitative risk assessment in support of the registration review of hymexazol. For a detailed discussion, see the *Hymexazol: Human Health Draft Risk Assessment in Support of Registration Review*, published on January 6, 2016 in the public docket EPA-HQ-OPP-2010-0127, which can be accessed on http://www.regulations.gov/.

1. Risk Conclusions

Dietary Assessment

Hymexazol is not considered a food use chemical as data show that it quickly metabolizes to carbon dioxide and is then incorporated into plant sugars after being taken up into the plant. Thus, dietary exposure via estimated concentrations in drinking water was considered

by the Agency. Acute and chronic dietary risk assessments (drinking water only) were performed incorporating modeled drinking water residues. The resulting acute and chronic drinking water estimates were below the Agency's level of concern (LOC) *i.e.,* less than 100% of either the acute or chronic reference dose (aRfD, and cRfD, respectively) for the U.S. population and all population subgroups. Therefore, both acute and chronic dietary exposure estimates are < 1% of the RfD for all population subgroups, and are not a risk concern.

Residential Assessment

There are currently no registered residential uses for hymexazol and no residential exposures are anticipated; thus, a residential assessment was not conducted.

Aggregate Assessment

Aggregate risk estimates take into account both dietary (food and drinking water) and residential sources of exposure. Because hymexazol has no registered residential uses and no residential exposure is expected, the aggregate exposure is equivalent to the dietary (drinking water only) exposure, which has been determined to be not of concern.

Spray Drift Assessment

Based on the use pattern and formulation, spray drift is not anticipated from seeds treated with hymexazol and thus a residential spray drift assessment was not completed.

Occupational Assessment

The occupational assessment estimates risk to handlers (those who mix, load, and apply a pesticide) and to workers (those who re-enter a treated area to perform tasks) in an occupational setting via the dermal and inhalation routes of exposure. Based on hymexazol use as a sugar beet seed treatment, short- and intermediate-term exposure durations were assessed for workers involved in treating and handling sugar beet seeds (*i.e.*, primary exposure to mixers, sewers, baggers, and individuals performing multiple activities) and workers planting the seed (secondary exposure). Post-application and long-term exposure scenarios were not assessed as exposure is expected to be negligible, because once the seed is planted there are essentially no further exposure scenarios.

Occupational risks of concern are those identified by an aggregate risk index (ARI) lower than one[1] (ARI < 1). The majority of occupational handler and applicator scenarios were not of concern based upon risk estimates that incorporate the personal protective equipment (PPE) identified on the hymexazol label (single layer of clothing and gloves for applicators, mixers and loaders; single layer of clothing for baggers and other handlers), and the maximum application

[1] Inhalation and dermal routes of exposure have been combined because the toxic effects are common between the inhalation and dermal routes of exposure. However, due to the lack of a subchronic inhalation study, the Agency has applied an additional database uncertainty factor of 10X, for the inhalation route of exposure (see section 4.4.1 of the *Hymexazol: Human Health Draft Risk Assessment in Support of Registration Review. D425247*.). This resulted in a different LOC for dermal (100) and inhalation (1000) exposures, thus requiring the use of an aggregated risk index (ARI) (verses a combined MOE approach) to conduct the occupational risk assessment.

rate (90g typical end-use product (TEP)/kg-seed). However, ARIs less than 1 were identified for two occupational scenarios:

(i) Mixers:
   a. with single layer of clothing, gloves, and no respirator (labelled PPE): ARI = 0.22
   b. with a double layer of clothing, gloves and no respirator: ARI = 0.23
   c. with a double layer of clothing, gloves, and a filtering face piece respirator (PF5 filter): ARI = 0.6

(ii) Multiple Activity Workers (person performing all seed treatment activities):
   a. with a single layer of clothing, gloves for loading/applying, no gloves for sewing/stacking, and no respirator (labelled PPE): ARI = 0.87

Thus, based on currently required PPE and assuming maximum application rates, workers mixing seed treatments and workers performing multiple activities for treated seed, resulted in ARIs below 1, and are risk estimates of concern.

Cumulative Effects

Section 408(b)(2)(D)(v) of the FFDCA requires the Agency to consider the cumulative effects of exposure to substances that have a common mechanism of toxicity. These considerations include the possible cumulative effects of such residues on infants and children. EPA has not made a common mechanism of toxicity finding for hymexazol and any other substances, and hymexazol does not appear to produce a toxic metabolite produced by other substances. Therefore, EPA has not assumed that hymexazol has a common mechanism of toxicity with other substances, and a cumulative effects assessment was not performed.

2. Food Tolerances

Plant metabolism data provides evidence that hymexazol is rapidly metabolised to carbon dioxide (CO_2) after systemic uptake, then is converted to sugars. Therefore, hymexazol is not considered a food-use chemical, and no food tolerances are established or are required for hymexazol.

3. Human Incidents

For this registration review, an incident search was completed in November 2009. There were no incidents identified in the Main and Aggregate Incident Data System (IDS) from 2002 to 2009 (*D371893, Updated Review of Hymexazol Incident Reports)*. An updated incident search was conducted in October 2015. There were no incidents identified in IDS from 2010 to 2015, or from SENSOR-pesticides from 1998-2011. For additional details, please refer to the *Hymexazol: Tier I Update Review of Human Incidents/Epidemiology for Draft Risk Assessment* in public docket EPA-HQ-OPP-2010-0127, which can be accessed at www.regulations.gov.

4. Human Health Data Needs

The hymexazol toxicological database is not complete, but was sufficient for conducting the human health risk assessment. In preparation for the human health risk assessment for hymexazol, the Office of Pesticide Program's Hazard and Science Policy Council (HASPOC)

met in October 2015 to discuss the absence of an inhalation toxicity study for hymexazol. Using a weight of evidence approach (WOE), the HASPOC determined that a subchronic developmental inhalation study is needed for hymexazol. In the absence of this data, an additional 10X database uncertainty factor has been applied to the inhalation route of exposure for assessing risks (TXR 0057244). The Agency intends to issue a DCI to obtain data for the subchronic inhalation study to fulfill this database uncertainty (see Appendix A).

B. Ecological Assessment

A summary of the Agency's ecological risk for hymexazol is presented below. For detailed discussions of all aspects of the ecological risk assessment, see the *Hymexazol: Ecological Risk Assessment for Registration Review*, published on January 6, 2016, in the public docket EPA-HQ-OPP-2010-0127, which can be accessed at http://www.regulations.gov/.

1. Environmental Fate and Exposure

The dominant dissipation mechanism for hymexazol is expected to be through biotransformation in both aerobic and anaerobic soils to CO_2 and methane with a half-life of 7.7 and 1.7 days, The *n*-octanol partition coefficient for hymexazol is very low (K_{ow} = 3.0), thus it is not expected to bioaccumulate in fish. Hymexazol is stable to hydrolysis (abiotic) and highly mobile (K_d from < 0.1 to 0.526 mL/g), and its mobility is expected to increase with pH. In addition, due to its vapor pressure (1.37 X 10^{-3} torr) and Henry's Law Constant value (2.74 x 10^{-9} atm-m^3/mol), hymexazol shows evidence of potential volatilization from dry soil (parent only).

2. Risk Conclusions

Overall, risks from hymexazol to non-target plants, amphibians, reptiles, aquatic animals and aquatic plants, and invertebrates are below the level of concern (LOC) and therefore not a risk concern. Risk concerns identified by the Agency include potential acute and chronic risks to birds and mammals from consumption of hymexazol-treated seeds. The effect observed in the mammalian study was reduced fetal weight and developmental delays, while for avian species, reduced egg-shell thickness was observed in both studies (one with bobwhite quail and another with mallard duck).

Risk to Terrestrial Organisms

Birds and Mammals

Potential acute and chronic risks to birds and mammals that may feed on treated seeds were identified for hymexazol's only use pattern. The Agency estimated both acute risk quotients (RQs) based on the LD_{50}, and chronic RQs based on the no observed adverse effect level (NOAEL). The Agency estimated RQs for a number of scenarios, including different application (seed treatment) rates and seeding rates. The following risk estimates are based on the maximum labelled application rate (90g TEP/kg-seed) and a maximum seeding rate (900,000 seeds/A). For mammals, there were LOC exceedances for all scenarios and all size classes. Acute RQs ranged from 0.01 to 3.81 (where the LOC = 0.5), and chronic RQs ranged from 27.91 to 60.95 (where

the LOC = 1). For birds, there were LOC exceedances for all scenarios and all size classes as well. Acute RQs ranged from 0.01 to 18.08 and chronic RQs were 164.23[2] for all size classes.

A second analysis, was conducted that expressed potential risk by estimating the number of hymexazol-treated seeds either a mammal or bird would need to consume to reach a dose equal to either the acute or chronic LOC, as well as the area that either a bird or mammal would need to glean to reach a dose equal to either the acute or chronic LOC (referred to as a Seed Consumption Approach (SCA)). The Agency found that the number of hymexazol-treated seeds a mammal needs to consume to reach the acute risk LOC (0.5) ranged from 42 seeds for small mammals to 977 seeds for large mammals, and the number of seeds needed to reach the chronic LOC (1) ranged from 5 to 122 (small to large mammals, respectively). Mammals would need to glean an area between 2 to 47 ft^2 to reach the acute LOC and glean an area between 0.25 to 6 ft^2 to reach the chronic LOC (small to large mammals, respectively). The number of hymexazol-treated seeds a bird needs to consume to reach the acute risk LOC ranged from 14 to 1263 (small to large birds, respectively) and the number of seeds a bird needs eat to reach the chronic LOC ranged from 3 to 39 (small to large birds, respectively). A bird would need to glean an area between 0.68 to 61 ft^2 to reach the acute LOC, and would need to glean an area between 0.15 to 2 ft^2 to reach the chronic LOC (small to large birds, respectively).

Terrestrial Plants

Due to the use pattern of hymexazol (seed treatment), spray drift is not expected, thus seedling emergence data was used to calculate RQs, as it is more representative than vegetative vigor data. There were no LOC (LOC = 1) exceedances as all RQs < 0.1 for applications at the highest rate. Given there are also no terrestrial plant incidents reported, the Agency does not expect effects to terrestrial plants.

Terrestrial invertebrates

The Agency has only limited data on terrestrial invertebrates and therefore did not conduct an assessment for this taxa. Only acute contact data (LC_{50}) and acute dietary data (LD_{50}) are available. Both the acute contact and acute oral values are greater than 100ug/bee, which suggests that the risk to honey bees on an acute basis is low.

3. Ecological Incidents

A search was conducted for ecological incidents involving hymexazol on February 11, 2015, using the Ecological Incident Information System (EIIS), the Aggregate Summary Module of OPP's Incident Database, and the Avian Monitoring Information System (AIMS). In the EIIS, AIMS, and Aggregate Summary Module, there were no incidents reported for hymexazol for the period January 1, 2010 to March 19, 2015. For additional details, please refer to the *Ecological Risk Assessment for Registration Review of Hymexazol* in public docket EPA-HQ-OPP-2010-0127, which can be accessed at www.regulations.gov.

[2] Endpoints are adjusted based on three size classes of birds and mammals; this adjustment is not conducted for chronic avian endpoints because data does not exist to incorporate scaling factors. Therefore chronic avian RQs are not scaled and thus do not change across size classes.

4. Ecological Effects Data Needs

When the registration review docket for hymexazol opened, EPA had not completed its risk assessment for pollinators and did not identify the need for any ecotoxicity studies to evaluate potential effects on pollinators. However, since the issuance of the June 2014 *Guidance for Assessing Pesticide Risks to Bees*[3], EPA has begun to require these data where applicable. EPA intends to issue a DCI to obtain the following data for hymexazol. The following studies are the studies, of the pollinator data requirement suite, for which EPA does not have for hymexazol and therefore identified as a data gap.

Guideline #	Study
Non-Guideline	Honey bee chronic oral toxicity, adult (Tier 1)*
Non-Guideline (OECD 237)	Honey bee acute oral toxicity, larvae (Tier 1)
Non-Guideline	Honey bee chronic oral toxicity, larvae (Tier 1)
Non-Guideline (OECD 75)	Honey bee Tier 2 Semi-Field Toxicity Testing (tunnel/enclosure or colony feeding) (Tier 2)**
Non-Guideline	Residues in Pollen and Nectar/Field Residue Analysis (Tier 2)**
850.3040	Field testing for pollinators (Tier 3)**

*: Tier 1 (laboratory-based studies)
**: Tier 2 and 3 (semi-field and full field colony-level studies). The need for higher tier tests for pollinators will be determined based upon lower-tiered tests and/or other lines of data and the need for a pollinator risk assessment.

5. Endangered Species Assessment

In November 2013, the EPA, along with the Services and the USDA, released a summary of their joint Interim Approaches for assessing risks to listed species from pesticides. The Interim Approaches[4] were developed jointly by the agencies in response to the National Academy of Sciences' (NAS) report recommendations, and reflect a common approach to risk assessment shared by the agencies as a way of addressing scientific differences between the EPA and the Services. The NAS report[5] outlines recommendations on specific scientific and technical issues related to the development of pesticide risk assessments that EPA and the Services must conduct in connection with their obligations under the ESA and FIFRA.

The joint Interim Approaches were released prior to a stakeholder workshop held on November 15, 2013. In addition, the EPA presented the joint Interim Approaches at the December 2013 Pesticide Program Dialogue Committee (PPDC) and State-FIFRA Issues Research and Evaluation Group (SFIREG) meetings. The agencies also held stakeholder workshops in April and October 2014, in April 2015, and in June of 2016, allowing additional opportunities for stakeholders to comment on the Interim Approaches. Additional workshops are

[3] http://www2.epa.gov/sites/production/files/2014-06/documents/pollinator_risk_assessment_guidance_06_19_14.pdf
[4] *Interim Approaches for National-Level Pesticide Endangered Species Act (ESA) Assessments Based on the Recommendations of the National Academy of Sciences April 2013 Report.* Available at http://www2.epa.gov/endangered-species/interim-approaches-pesticide-endangered-species-act-assessments-based-nas-report
[5] *Assessing Risks to Endangered and Threatened Species from Pesticides*. National Academy of Sciences. 2013. Available from http://www.nap.edu/catalog.php?record_id=18344

planned to enhance stakeholder involvement. As part of a phased, iterative process for developing the Interim Approaches, the agencies will also consider public comments on the Interim Approaches in connection with the development of upcoming registration review decisions. The details of the joint Interim Approaches are contained in the white paper *Interim Approaches for National-Level Pesticide Endangered Species Act (ESA) Assessments Based on the Recommendations of the National Academy of Sciences April 2013 Report*[6], dated November 1, 2013.

Given that the agencies are continuing to develop and work toward implementation of the Interim Approaches to assess the potential risks of pesticides to listed species and their designated critical habitat, the ecological risk assessment supporting this proposed interim registration review decision for hymexazol does not contain a complete ESA analysis that includes effects determinations for specific listed species or designated critical habitat. Although EPA has not yet completed effects determinations for specific species or habitats, for this proposed interim decision, EPA's evaluation assumed, for all taxa of non-target wildlife and plants, that listed species and designated critical habitats may be present in the vicinity of the application of hymexazol-treated sugar beet seeds. This assessment allows EPA to focus its future evaluations on the types of species where the potential for effects exists once the scientific methods being developed by the agencies have been fully vetted. Once the Agencies have fully developed and implemented the scientific methodology for evaluating risks for listed species and their designated critical habitats, these methods will be applied to subsequent analyses for hymexazol as part of completing the final registration review decision.

C. Endocrine Disruptor Screening Program

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent registration decision for hymexazol, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), hymexazol is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the

[6] Available at https://www.epa.gov/endangered-species/implementing-nas-report-recommendations-ecological-risk-assessment-endangered-and

statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[7] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors. Hymexazol is not included on List 1 or List 2. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[8]

In this proposed interim decision, EPA is making no human health or environmental safety findings associated with the EDSP screening of hymexazol. Before completing this registration review, the Agency will make an EDSP FFDCA section 408(p) determination.

D. Benefits and Rate Information

Hymexazol reduces damping off[9] in young seedlings and enables stand establishment in sugar beet production areas that have pressure from fungal pathogens such as *Aphanomyces* and *Pythium* spp. Between 2010 and 2014, hymexazol-treated sugar beet seeds were planted on approximately 218,000 acres. *Aphanomyces* spp. is a well-recognized pest for sugar beet seeds all over the world, and can cause total yield loss or severely reduce the quality of the crop. Hymexazol is currently the only chemical control registered for use on sugar beet seeds to control *Aphanomyces* spp. Hymexazol is also effective at controlling *Pythium* spp. which can cause both pre-emergence and post-emergence damping-off. Other active ingredients recommended to control *Pythium* spp. in sugar beets include metalaxyl and mefenoxam, both of which are in the high risk category for pathogen resistance. Hymexazol-treated sugar beet seeds can be used in areas with fungicide-resistant *Pythium* spp. and used in combination with other fungicides to prevent development of resistance.

The United States Department of Agriculture (USDA) and the technical registrant for hymexazol (Mitsui) provided current usage and agricultural practice information. This allowed the Agency to better understand how seeding and application rates assessed from the hymexazol label compare to actual crop production practices. Regarding the application rates, USDA

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[7] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.

[8] http://www.epa.gov/endo/

[9] Damping off is a horticultural disease or condition caused by a number of different pathogens that kill or weaken seeds or seedlings before or after they germinate, it usually refers to the rotting of stem and root tissues at and below the soil surface and is most prevalent in wet and cool conditions.

indicated that rates between 20g TEP/kg-seed and 30g TEP/kg-seed are used in most areas, 45g TEP/kg-seed is recommended in areas with high disease pressure, and rates up to 90g TEP/kg-seed are not advised. This was consistent with use rate information provided by the registrant. They indicated that the majority (65-100%) of sugar beet seed is treated with between 20 g TEP/kg-seed and 35g TEP/kg-seed dependent on the disease pressure, a small percentage of (10-20%) is teated with 45g TEP/kg-seed in heavy disease pressure areas, and none are treated with the 90g TEP/kg-seed rate. This suggests that the 45g TEP/kg-seed and lower are the most relevant rates while assessments based on the 90g TEP/kg-seed may not represent current usage scenarios.

Regarding seeding rates, USDA information[10] indicated that rates can vary between 40,000 seed/A and 60,000 seed/A, contingent on the area of the country and row spacing used by sugar beet growers, but most (70%) sugar beet production is grown with a seeding rate of approximately 50,000 seeds/A. According to registrant information, seeding rates range from 55,000 to 63,000 seed/A, with an average being 57,000 seeds/A. Therefore, seeding rates used in the ecological risk assessment (200,000 to 900,000 seeds/A) may be overestimates as they relate to the current planting practices for hymexazol-treated sugar beet seeds, which may be closer to 60,000 seeds/A.

Due to its targeted application and usefulness against sugar beet seeds prone to fungal infection, hymexazol is an important tool for growers to have as part of their Integrated Pest Management (IPM) programs. In addition, the application rates modelled in the ecological and human health risk assessments should be considered in the context of the information outlined above as they may be more realistic sugar beet seed treatment and planting practices with hymexazol. For more information on the benefits and usage of hymexazol, see *Hymexazol Benefits Information (PC # 129107)* in the public docket EPA-HQ-OPP-2010-0127 at www.regulations.gov.

IV. Risk Characterization and Proposed Interim Registration Review Decision

As discussed in Section III of this document, human health risks were identified from occupational exposures, and ecological risks were identified from LOC exceedances for birds and mammals. To better understand the estimated risks, the Agency provides characterization by using alternative scenarios, assumptions, and inputs to explore how or whether estimates of risk change.

A. Human Health Risk Characterization

Occupational Risks

As discussed in Section III of this document, LOC exceedances for occupational workers were demonstrated by an ARI < 1. When estimating occupational risks from hymexazol, the

[10] USDA. 2016. USDA OPMP personal communication, see EPA document, Hymexazol Benefits Information, dated Sep 7,2016.

Agency lacked chemical-specific worker exposure data, but relied on surrogate data and default assumptions from the Agency's pesticide handlers database[11] (PHED). The Agency assessed the maximum application rate (90g TEP/kg-seed), lower rates identified on the label were not modeled. However, as noted above, information from the technical registrant and the USDA indicate that the 90g TEP/kg-seed application rate is not used. Information on the product label characterizes the application rate above 45 grams in this way: "Use of rates greater than 45 grams Tachigaren 70 WP per unit of seed may result in phytotoxicity. Use of rates greater than 45 grams is not recommended except under conditions of, or in fields with a known history of heavy disease pressure." The technical registrant indicated that the 90g TEP/kg-seed rate was placed on the label for rare instances of exceedingly high disease pressure. Consistent with the technical registrant's characterization, the USDA was not able to provide any evidence of use of the 90g TEP/kg-seed application rate. Since occupational MOEs are linearly (and inversely) related to the application rate, estimated ARIs for occupational individuals (mixers and individuals performing multiple activities) at 45g TEP/kg-seed are double those estimated using 90g TEP/kg-seed.

Table 1: Occupational Risk Calculations at 90g TEP/kg-seed and 45g TEP/kg-seed

PPE Level	**ARI (based on 90g TEP/kg-seed)**	**ARI (based on 45g TEP/kg-seed)[12]**
Mixers		
Single layer, gloves, no respirator	0.22	0.44
Double layer, gloves, no respirator	0.23	0.46
Double layer, gloves, filtering face piece respirator (PF5 filter)	0.6	1.20
Multiple Activity Workers (workers performing all activities)		
Single layer, gloves (loader/applicator), no respirator	0.87	1.74

As noted above in Table 1, estimates of risk for the individual performing multiple activities is above 1 at 45g TEP/kg-seed, and no longer a risk concern. Risks to mixers are also above 1 when a double layer of clothing, gloves and a filtering face piece respirator (PF5 filter) are worn. Also seen in the estimates above, is the decrease in exposure and estimated risk provided by the filtering face piece respirator (PF5 filter) compared to decrease in exposure and estimated risk provided by a second layer of clothing. The ARI moved from 0.44 to 0.46 with the addition of a second layer of clothes, and from 0.46 to 1.20 with the addition of a filtering face piece respirator (PF5 filter) .Therefore, to further characterize risks to mixers and explore PPE options, the Agency looked at risk to mixers with a single layer of clothing, gloves, and a filtering face piece respirator (PF5 filter).

[11] More information on EPA Pesticide Handlers Exposure Database can be found at: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

[12] ARI = Aggregate Risk Index = 1÷ [Dermal LOC ÷ Dermal MOE) + (Inhalation LOC ÷ Inhalation MOE)]. Exposure is directly proportional to application rate, and the MOE is inversely proportional to exposure, thus a rate reduction of 50% will equate to an ARI increase of 50%. Exposure (mg/kg-bw-day) = unit [exposure (mg pest/lb a.i. applied) x application rate (lbs. a.i./Acre x Acres/day x 1/bw] and MOE (margin of exposure) = Point of Departure (e.g., NOAEL) ÷ Exposure.

Mixers:

(i) With single layer of clothing, gloves and a filtering face piece respirator (PF5 filter) (at 90g TEP/kg-seed): ARI = 0.50

(ii) With single layer of clothing, gloves and a filtering face piece respirator (PF5 filter) (at 45g TEP/kg-seed): ARI = 1.0

The ARI increases to 1 when a mixer is wearing a single layer of clothing, gloves and a filtering face piece respirator (PF5 filter),and thus does not exceed the Agency's level of concern. The cost of requiring a filtering face piece respirator (PF5 filter) for mixers was taken into consideration as part of the risk-benefit analysis for this proposed interim decision. The Agency also notes that costs may range up to $234 per mixer (inclusive of a fit test, medical qualification and training) and would vary considerably between seed treatment facilities due to the number of workers. For details of the economic costs of respirators as well as the overall benefits of hymexazol, see *Hymexazol Benefits Information (PC # 129107)* in the docket EPA-HQ-OPP-2010-0127 at www.regulations.gov.

B. Ecological Risk Characterization

Acute and Chronic Mammalian and Avian Risks

The Agency identified LOC exceedances for birds and mammals, with acute RQs ranging from <LOC to 3.81 (mammals) and <LOC to 18.1 (birds), and chronic RQs ranging from 9.3 to 60.95 (mammals), and from 54.75 to 164.23 (birds). The following discussion is provided to explain several assumptions of the risk estimation in order to provide greater context to these estimates.

Hazard

For both avian and mammalian hazard, the acute endpoint used is mortality (LD_{50}), and the chronic endpoint used is based on reproductive effects. For birds, the chronic endpoint identified was reduced eggshell thickness seen in two chronic avian studies. In the study with the bobwhite quail, the lowest observed adverse effect concentration (LOAEC) was indicated with a 5% effect level relative to the control, without any other observable treatment-related effects. In the second study with mallard duck, the LOAEC was indicated with an 8.35% effect level of reduced egg shell thickness relative to the control. In both studies, the LOAEC was identified at the highest dose tested. Both the study with the mallard duck and the bobwhite quail have dosing periods of approximately 16-25 weeks. With respect to chronic mammalian hazard, the chronic endpoint identified, reduced fetal weight and evidence of other developmental abnormalities, with a 9.3% effect level at the lowest observed adverse effect level (LOAEL). The chronic hazard was drawn from a teratogenicity study with a dosing period of approximately 9 days.

While the Agency always estimates RQs based on the NOAEL, it can also characterize the potential risk by estimating RQs using the LOAEL. Estimated RQs based on the LOAEL convey potential risk based upon actual observed effect(s) seen in the study. However, estimated risk based upon the LOAEL does not provide a margin of safety that is afforded by the NOAEL.

Exposure

The Agency presented a range of RQs for hymexazol to account for different seeding rates and different application rates as indicated by the label. However, based upon information from both USDA and the technical registrant, as dicussed in Section D above, the Agency reasons that the most environmentally relevant RQs may be those based on exposure estimates derived from the low application rate (up to 45g TEP/kg-seed) and the low seeding rate (4.8 lb seed/A which approximates to 2000,000 seed per acre).

With respect to the application rate, information provided by the USDA and technical registrant indicates that there is little or no sugar beet seed treated at 90g TEP/kg-seed, a portion of hymexazol-treated seed is treated at the 45g TEP/kg-seed rate, and approximately half of the hymexazol-treated seed is treated at or below the 35g TEP/kg-seed rate (*Hymexazol Benefits Information (PC #129107)).*

With respect to the seeding rate, USDA information indicated that most sugar beet production is grown with a seeding rate of approximately 50,000 seeds/A, while the average seeding rate provided by the registrant was 57,000 seeds/A. Therefore, information from both USDA and the technical registrant suggests that even the lower end of the seeding rates used by the Agency (4.8 lb seed/A which approximates to 200,000 seeds per acre) may be a conservative estimate. Consequently, when looking across the range of estimated RQs for hymexazol, those RQs that employ the lower end of the application rate (30 - 45g TEP/kg-seed) and the lower end of the seeding range (4.8 lb seed/A) may better reflect the current use of hymexazol.

A summary of selected RQs, based on lower application rates and lower seeding rates, and using the NOAEL and LOAEL is presented below in Tables 2 and 3 and indicate lower RQs than those cited above in Section B. As noted in Tables 2 and 3, for mammals, estimated acute risks range from < LOC – 1.90, and estimated chronic risks range from 9.30 – 30.48; and, for birds estimated acute risks range from < LOC – 9.04 and estimated chronic risks range from 54.75 – 82.12.

Table 2. Selected Estimated Mammalian RQs Based on Low Application Rates and the Low Seeding Rate (Source: Table 14 of *Hymexazol: Ecological Risk Assessment for Registration Review*)

App Rate / Seed Rate	Acute # 1 Dietary Estimate	Acute # 2 LD_{50}/ft^2 Estimate	Chronic NOAEL	Chronic LOAEL
15 gram mammal				
45g TEP/kg-seed/ 4.8 lb. seed/A	1.90	0.03	30.48	6.10
30g TEP/kg-seed /4.8 lb. seed/A	1.27	0.02	20.32	4.06
35 gram mammal				
45g TEP/kg-seed/ 4.8 lb. seed/A	1.63	0.02	26.03	5.21
30g TEP/kg-seed /4.8 lb. seed/A	1.08	0.01	17.36	3.47
1000 gram mammal				
45g TEP/kg-seed/ 4.8 lb. seed/A	0.87	< 0.01	13.95	2.79
30g TEP/kg-seed /4.8 lb. seed/A	0.58	<0.01	9.30	1.86

Acute LOC = 0.5
Chronic LOC = 1

Table 3. Selected Estimated Avian RQs Based on Low Application Rates and Low Seeding Rate (Source: Table 15 of *Hymexazol: Ecological Risk Assessment for Registration Review)*				
App Rate / Seed Rate	**Acute #1 Dietary Estimate**	**Acute # 2 LD_{50}/ft^2 Estimate**	**Chronic NOAEC**	**Chronic LOAEC**
20 gram bird				
45g TEP/kg-seed /4.8 lb. seed/A	9.04	0.09	82.12	32.86
30g TEP/kg-seed/4.8 lb. seed/A	6.03	0.06	54.75	21.91
100 gram bird				
45g TEP/kg-seed /4.8 lb. seed/A	4.05	0.01	82.12	32.86
30g TEP/kg-seed/4.8 lb. seed/A	2.70	0.01	54.75	21.91
1000 gram bird				
45g TEP/kg-seed /4.8 lb. seed/A	1.28	< 0.01	82.12	32.86
30g TEP/kg-seed/4.8 lb. seed/A	0.86	< 0.01	54.75	< 0.01

Acute LOC = 0.5
Chronic LOC = 1

Refined Analysis for Seed Incorporation in Soil

In estimating risk to birds and mammals from consuming hymexazol-treated seed, the Agency presented two analyses, an RQ analysis, and a Seed Consumption Approach (SCA). The Agency's acute RQ analyses expresses potential risk using two different methods, and presents chronic risk through one RQ estimate. One of the Agency's acute RQ estimates for birds and mammals (Acute RQ #2; LD_{50}/ft^2 estimate) reflects potential risk based upon the amount of pesticide-treated seed that may be available. The LD_{50}/ft^2 estimate uses inputs such as seeding rate and other variables to capture bioavailability of a pesticide. The other acute risk estimate (Acute RQ #1; dietary risk estimate) does not consider how much pesticide-treated seed may or may not be available, but rather estimates potential risk based upon an assumption that an organism satisfies its entire daily caloric need from consuming only hymexazol-treated sugar beet seed. The Agency's chronic risk estimate is similar to this dietary risk estimate, except that it compares the potential exposure to a NOAEC or NOAEL (chronic) instead of an LD_{50} (acute). The Agency's SCA looks at: (i) how many seeds are needed to reach the LOC; and (ii) how many square feet a bird or mammal must glean in order to reach the LOC. These analyses are summarized in Section III above and are discussed in full in EPA's, *Hymexazol: Ecological Risk Assessment for Registration Review, (Jan 6, 2016).* However, at the time the Agency completed the Hymexazol Ecological Risk Assessment, neither of the analyses accounted for reduced exposure and potential risk as a result of hymexazol-treated seed being planted below the soil surface, or incorporated, and therefore of limited availability for either birds or mammals.

Based upon recently released guidance[13], the Agency refined the hymexazol RQ estimates and hymexazol SCA to account for the soil incorporation of pesticide-treated seed. Because sugar beet seeds are planted at a depth of 0.75 – 1.0 inch, the Agency estimates that approximately 99% of the seed is incorporated, leaving only 1% of hymexazol-treated seed available on the soil surface for possible consumption by a bird or mammal (sugar beet seed is typically planted using precision agriculture equipment and not broadcast onto the surface). Tables 4 and 5 below show that if incorporation is taken into account, and only 1% of the planted seed is available, potential risk expressed through Acute RQ #2, (LD_{50}/ft^2 estimate) are below the LOC. However, potential risk expressed through Acute RQ #1 and chronic risk (the dietary risk estimates) are still indicated, because computationally, these do not reflect what portion of pesticide-treated seed may be available above the soil. While potential acute dietary risk is predicted, the analysis using the LD_{50}/ft^2 estimate suggests actual exposure and thus risk are expected to be lower. Due to the nature of their calculations the Acute RQ#1 and chronic risk RQ do not change as a result of 99% seed incorporation, however, the refined analysis demonstrates that the number of square feet a bird or mammal needs to glean to reach the LOC increases 2-fold. Tables 4 and 5 present refined risk estimates when incorporation of seed is accounted for. Tables 4 and 5 only present estimates for the small bird and small mammal because risk to small species represent the worst-case scenario.

Table 4. Refined Analysis to Account for Seed Incorporation in Soil for Small Mammal (45g TEP/kg/seed; seeding rate of 218,000 seeds per acre)

Acute					**Chronic**		
Acute Risk RQ		**Refined Analysis - Acute**			**Chronic Risk RQ**	**Refined Analysis - Chronic**	
Acute RQ #2; LD_{50}/ft^2 Estimate	Acute RQ #2; LD_{50}/ft^2 Estimate (with 99% incorporation)	Acute RQ #1; Dietary Risk Estimate (does not change since seed availability is not taken into consideration)	Area Needed to be Gleaned to Reach LD_{50} (ft^2)	Area Needed to be Gleaned to Reach LD_{50} (ft^2) (with 99% incorporation)	Chronic Dietary Risk Estimate (does not change since seed availability is not taken into consideration)	Area needed to be Gleaned in order to reach Chronic NOAEL (ft^2)	Area Needed to be Gleaned to Reach Chronic NOAEL(ft^2) (with 99% incorporation)
0.03	0.0003	1.90	16.71 ft^2	1671 ft^2	30.48	2.09 ft^2	209 ft^2

[13] See EPA's *Refinements for Risk Assessment for Pesticide Treated Seeds – Interim Guidance* at: https://www.epa.gov/sites/production/files/2016-04/documents/interimseedtreatmentguidance2016.pdf

Table 5. Refined Analysis to Account for Seed Incorporation in Soil for Small Bird (45g TEP/kg/seed; seeding rate of 218,000 seeds per acre)							
Acute					**Chronic**		
Acute Risk RQ		**Refined Analysis - Acute**			**Chronic Risk RQ**	**Refined Analysis – Chronic**	
Acute RQ #2; LD_{50}/Ft^2 Estimate	Acute RQ #2; LD_{50}/Ft^2 Estimate (with 99% incorporation)	Acute RQ #1; Dietary Risk Estimate (does not change since seed availability is not taken into consideration)	Area Needed to be Gleaned to Reach LD_{50} (ft^2)	Area Needed to be Gleaned to Reach LD_{50} (ft^2) (with 99% incorporation)	Chronic Dietary Risk Estimate (does not change since seed availability is not taken into consideration)	Area needed to be Gleaned in order to reach Chronic NOAEL (ft^2)	Area Needed to be Gleaned to Reach Chronic NOAEL(ft^2) (with 99% incorporation)
0.09	0.0009	9.04	5.61 ft^2	561 ft^2	82.12	1.23 ft^2	123 ft^2

The refined analysis puts context around the potential risks by attempting to reflect the likelihood of exposure if incorporation is considered. The refined analysis also highlights that the dietary based RQs (Acute RQ #1 and chronic RQ) may not be the most appropriate tool to express potential risk from hymexazol-treated sugar beet seed. The refined SCA however does make up for what the dietary based RQs lack, by presenting potential risk in terms of *area needed to be gleaned* to reach either the acute or chronic LOC, which can account for soil incorporation. When one considers the values for the *area needed to be gleaned*, and notes that these areas (*e.g.*, 209 ft^2 for a small mammal and 123 ft^2 for a small bird, for chronic risk) are smaller than the area in which an animal of this size typically forages[11,14], then potential exposure and risk cannot be excluded. This provides a way to quantify the plausibility of exposure and thus risk, because if the area needed to be gleaned to reach the LOC is smaller than the animal's typical foraging area, then risk is possible. For details on this refined analysis see *Hymexazol: Risk Refinement and Build-up Pellet Recalculation for Mammals and Birds for the Ecological Risk Assessment for Registration Review* in the public docket EPA-HQ-OPP-2010-0127 at www.regulations.gov.

Finally, a note regarding the temporal and spatial components of potential chronic exposure, and therefore risk, from hymexazol-treated sugar beet seed. When estimating risk, the Agency attempts to match the duration of the hazard endpoint with the duration of the exposure estimate, such as using a chronic endpoint (a NOAEL) and comparing that with a chronic exposure value (an average). As discussed above, the NOAEL is drawn from a chronic study, which is designed to identify effects elicited from low doses administered over extended periods. Low doses received over extented periods may be comparable to average exposure values rather than to peak exposure values (note that the dosing period in the studies from which the hymexazol chronic endpoints were derived are 9 days long for mammals and 16-25 weeks long for birds). However, for chronic risk to birds and mammals, the Agency compares the NOAEL to a single-day, peak exposure value. By comparing a NOAEL to a peak exposure estimate, the chronic risk estimate for hymexazol may be an overestimate of potential risk; however, because

[14] Estimates of an organisms home range is presented in EPA's *Refinements for Risk Assessment for Pesticide Treated Seeds.* Home range is characterized as the area of a species movement over time. Over time, a small mammal may move over an area greater than 16,000ft^2, and small birds may move over an area greater than 150,000ft^2 .

toxicity studies are not designed to show when a chronic effect would occur relative to a certain exposure time, the use of the NOAEL remains protective of this uncertainty.

The Agency notes that there is some evidence that chronic risks from hymexazol may indeed be lower than what is estimated by the chronic RQ because the various spatial and temporal bounds of the use pattern and agronomic practices that go along with the use of hymexazol on sugar beet seed. For example, sugar beets are grown in 14 states, the majority of which have planting times from early April to May, and so potential hymexazol exposure to hymexazol-treated seed is not nationwide, as both the geographic coverage (number of states where sugar beets are grown) and duration of time sugar beet seeds are available for consumption is short. Further, the amount of hymexazol in exposed seed may breakdown due to environmental conditions following day zero and while germination times vary, most sugar beet seed typically germinates within several days, after which point they are no longer viable for consumption.

The Agency's risk estimates are intended to be protective so as to not underestimate risk and account for uncertainties based on the available dataset. The Agency also acknowledges that numerous variables affect potential ecological exposure and risk, and many are difficult, or simply cannot be reflected in the Agency's risk estimates. For this reason, a risk characterization discussion is included to better understand the variables that affect risk. While the Agency's ecological risk assessment identified potential acute and chronic risks to birds and mammals, when the estimated risks are characterized with incorporation, temporal and spatial variables of sugar beet production, as well as the protective nature of its analysis, the Agency reasons that the potential for either acute or chronic risk to birds and mammals exists, but is likely lower than predicted.

C. Proposed Risk Mitigation Measures

The Agency identified potential risks to birds and terrestrial mammals, but believes that such risks may be lower than predicted. The Agency also found risks to occupational handlers including mixers, and individuals performing multiple activities when handling hymexazol to treat sugar beet seed. The Agency also believes that the availability of hymexazol represents a benefit to the sugar beet grower since hymexazol is considered the primary tool to protect sugar beet seed and seedlings from *Aphanomyces* spp. and *Pythium* spp. In order to reduce human health risks, reduce potential ecological exposure, and maintain the benefits of hymexazol, the Agency discussed mitigation measures with the technical registrant, and is proposing to: (i) reduce the maximum application rate by 50% (from 90g TEP/kg-seed to 45g TEP/kg-seed), and (ii) require a filtering face piece respirator (PF5 filter) for individuals engaged in the process of creating hymexazol-treated sugar beet seed.

The Agency reasons that removal of the 90g TEP/kg-seed application rate from labels will bring the modeled exposure for individuals performing multiple activities to a level where risks are no longer of concern (see Section IV, A). A reduction of the maximum application rate from 90g to 45g TEP/kg-seed will also reduce potential acute and chronic risks to birds and mammals. As discussed in Section IV above, when occupational risks to mixers were estimated at 45g TEP/kg-seed, the mixer used a single layer of clothes, gloves and a filtering face piece respirator (PF5 filter), the ARI = 1.

To mitigate potential inhalation risk to occupational handlers, the Agency is proposing requiring a respirator and associated fit test, training, and medical evaluation for the following:

- Individuals mixing hymexazol seed treatments (Mixer scenarios)

The EPA has recently required fit testing, training, and medical evaluations[15] for all handlers who wear respirators and whose work falls within the scope of the Worker Protection Standard.[16] If a hymexazol handler currently does not have a respirator, an additional cost will be incurred by the handler or the handler's employer, which includes the cost of the respirator plus the cost for a respirator fit test, training, and medical exam.

Respirator costs are extremely variable depending upon the protection level desired, disposability, comfort, and the kinds of vapors and particulates being filtered. Based on available information that EPA has, the average cost of a disposable PF10 respirator (filtering facepiece) is about $5 and a PF10 respirator (elastomeric half-face respirator) is $35, with their replacement cartridges averaging around $19.[17] The Agency believes that the average cost of a PF5 respirator is lower than the average cost of a PF10 respirator. The estimated cost of a respirator fit test, training and medical exam is about $180 annually.[18] The impact of the proposed respirator requirement is likely to be substantially lower for a hymexazol handler who is already using a respirator because the handler or handler's employer uses other chemicals requiring a respirator in the production system or as part of the business (*i.e.*, the handler or employer will only incur the cost of purchasing filters for the respirator on a more frequent basis). Respirator fit tests are currently required by the Occupational Safety and Health Administration (OSHA) for other occupational settings to ensure proper protection.[19] EPA acknowledges that requiring a respirator and the associated fit testing, training, and medical evaluation places a burden on handlers or employers. However, the proper fit and use of respirators is essential to accomplish the protections respirators are intended to provide. In estimating the inhalation risks, and the risk reduction associated with different respirators, EPA's human health risk assessments assume National Institute for Occupational Safety and Health (NIOSH) protection factors (*i.e.*, respirators are used according to OSHA's standards). If the respirator does not fit properly, use of hymexazol may cause unreasonable adverse effects on the pesticide handler.

The Agency considered the costs of its proposed mitigation measures. The Agency believes that the requirement of a filtering face piece respirator (PF5 filter) may increase cost to seed treatment facilities as a filtering face piece respirator (PF5 filter) can be approximately $5-$34, while the replacement cartridges average $19 each. In addition, a fit test for a respirator can

[15] Fit testing, training, and medical evaluations must be conducted according to OSHA regulations 29 CFR 1910.134, 29 CFR 1910.134(k)(1)(i) through(vi), and 29 CFR 1910.134, respectively.
[16] 40 CFR 170 (see also Appendix A of chapter 10 of the Label Review Manual, https://www.epa.gov/pesticide-registration/label-review-manual)
[17] Gempler's. 2016. Commercial-Grade Outdoor Work Gear Online Catalogue. Accessed online on August 26, 2016 at http://www.gemplers.com/respirators
[18] Economic Analysis of the Agricultural Worker Protection Standard Revisions. Biological and Economic Analysis Division, Office of Pesticide Programs, U.S. EPA. 2015. 205 p. Available at www.regulations.gov, docket number EPA-HQ-OPP-2011-0184-2522
[19] 29 CFR 1910.134

cost up to $180 per person per year. However, the Agency does not anticipate significant economic costs to growers from the reduced application rate because, based upon information from both the technical registrant and the USDA, the 90g TEP/kg-seed application rate is rarely, if ever, used, and consequently, a rate reduction from 90g to 45g TEP/kg-seed is not likely to impact a sugar beet growers' pest management costs, or yields.

In addition, as part of the hymexazol registration review, the Agency reviewed existing labels in light of EPA Label Review Manual (LRM). To ensure compliance with the LRM, the Agency is proposing certain changes or updated to pesticide products containing hymexazol.

D. Proposed Interim Registration Review Decision

The Agency initiated the hymexazol registration review in March 2010, and issued the registration review GDCI in October 2011. All data requirements of the hymexazol registration review GDCI have been satisfied, and the Agency completed draft human health and ecological risk assessments. In accordance with 40 CFR Sections 155.56 and 155.58, the Agency is issuing this proposed interim registration review decision. Except for the EDSP, ESA and pollinator components of this case, the Agency has made the following proposed interim registration review decision, see Appendix C.

Proposed Labeling for Mitigation

In order to reduce risk to occupational handlers, birds and mammals:

(1) The maximum application rate for products with hymexazol is proposed to be reduced from 90g TEP/kg-seed to 45g TEP/kg-seed; and

(2) a filtering face piece respirator (PF5 filter) is proposed to be required for persons mixing hymexazol for application to sugar beet seed.

Proposed Label Changes Consistent with the Label Review Manual (LRM)

Pesticide registrants are required to ensure that their product labels are current with Agency policies, such as the LRM. For more information on the LRM please refer to: https://www.epa.gov/pesticide-registration/label-review-manual. As part of the hymexazol registration review, the Agency reviewed hymexazol labels against chapter 18 of the LRM (Uniqe Product Labeling) and identified the following updates/changes for pesticide products that contain hymexazol.

Label Statements Based on Risk Assessment:

Based on EPA risk assessments and in accordance with safe handling, the following statements are proposed to be required on containers containing hymexazol-treated seed under the Environmental Hazards section.

"The U.S. EPA requires the following statements on containers containing seed treated with hymexazol:

- *Treated seeds exposed on soil surface may be hazardous to wildlife. Cover or collect treated seeds spilled during loading and planting. Treated seed must be incorporated into the soil*
- *Dispose of all excess treated seed by burying seed away from bodies of water.*
- *Do not contaminate water bodies when disposing of planting equipment wash waters.*
- *Do not allow children, pets or livestock to have access to treated seeds.*
- *Dispose of seed packaging or containers in accordance with local requirements."*

Label Statements for Exemptions to Dye Requirements:

Hymexazol is intended for commercial seed treatment only, and does not have a tolerance or tolerance exemption, and to be consistent with the LRM, the Agency is proposing the following be added to the Directions for Use section:

> *"Note: This product does not contain dye and is not covered by an appropriate tolerance, tolerance exemption, or other clearance under the Federal Food, Drug and Cosmetic Act. To comply with 40 CFR 153.155, therefore, all seed treated commercially with this product must be colored with an EPA-approved dye or colorant of a suitable color to prevent accidental use as food for man or feed for animals."*

Label Statements Associated with the Federal Seed Act:

Pesticide products containing hymexazol should be consistent with the current U.S. EPA LRM refer to https://www.epa.gov/sites/production/files/2015-03/documents/chap-18-sep-2013.pdf, Commercial seed labels for treated seeds, as distinct from seed treatment pesticide product labels, are required to comply with both the Federal Seed Act (FSA) and USDA's regulations concerning the labeling of treated seed (as found in the *Federal Seed Act* and *7 CFR Part 201*). The following statements must be on containers containing hymexazol-treated seed under the Directions for Use section:

> *"The Federal Seed Act requires that bags containing seed treated with this product shall be labeled with the following information: "The seed has been treated with hymexazol. Do not use for food, feed or oil purposes"*

General Label Stewardship

The registrant should ensure the following information is on all pesticide products containing hymexazol:

- Formulation type;
- Pounds of active ingredient (ai) per gallon of product;
- Ensure that the application rates expressed (i.e. lbs TEP/unit of seed) present maximum amount of ai for the subject product, or any other product with the subject ai;
- Use sites and permitted applicators, include any prohibitions of a user type;

- Application equipment;
- Glove statements – the appropriate gloves must be listed out on the label, per LRM (Chapter 10). Registrants can no longer reference the category charts; and
- Precautions should be separate from use restrictions (such as rotational crop restrictions, or restrictions for adjuvants and/or surfactants)

Consistent with EPA's June 2014 Guidance for Assessing Pesticide Risks to Bees, EPA is requiring pollinator data where applicable. EPA intends to issue a DCI to obtain these data for hymexazol. In the near future, EPA will provide further information and guidance on this effort. In addition, the Agency has determined that a subchronic inhalation study is required. These studies that will be required are included in Appendix A. The Agency intends to issue a DCI for those data to further inform risk assessment.

In this proposed interim registration review decision, EPA is making no human health or environmental safety findings associated with the EDSP screening of hymexazol, nor is it making a complete endangered species finding. The Agency's final registration review decision for hymexazol will depend upon the result of an ESA determination and any necessary Section 7 consultation with the Services, an EDSP FFDCA section 408(p) determination and the completion of a pollinator risk assessment.

V. NEXT STEPS AND TIMELINE

A. Interim Registration Review Decision

A Federal Register Notice will announce the availability of this proposed interim registration review decision for hymexazol and allow a 60-day comment period. If there are no significant comments or additional information submitted to the docket during the comment period that leads the Agency to change its proposed interim decision, EPA may issue an interim registration review decision for hymexazol. Once the interim registration review decision is issued, the hymexazol registrants must submit amended labels that include the label changes described in Appendix B. The revised labels must be submitted to the Agency for review within 60 days following issuance of the Interim Registration Review Decision. The mitigation measures and required label amendments are described in Appendices B and C below.

B. Final Registration Review Decision

A final decision on the hymexazol registration review case will occur after 1) EDSP FFDCA section 408 (p) determination, 2) an endangered species determination under ESA and any needed Section 7 consultation with the Services, and 3) an assessment of non-target exposure to pollinators.

Appendix A. Summary of Data Requirements for Hymexazol

Guideline	Study
Non-Guideline	Honey bee chronic oral toxicity, adult (Tier 1)*
Non-Guideline (OECD 237)	Honey bee acute oral toxicity, larvae (Tier 1)*
Non-Guideline	Honey bee chronic oral toxicity, larvae (Tier 1)*
Non-Guideline (OECD 75)	Honey bee Tier 2 Semi-Field Toxicity Testing (tunnel/enclosure or colony feeding) (Tier 2)**
Non-Guideline	Residues in Pollen and Nectar/Field Residue Analysis (Tier 2)**
850.3040	Field testing for pollinators (Tier 3)**
870.3465	90-Day inhalation toxicity

*: Tier 1 (laboratory-based studies)
**: Tier 2 and 3 (semi-field and full field colony-level studies). The need for higher tier tests for pollinators will be determined based upon lower-tiered tests and/or other lines of data and the need for a pollinator risk assessment.

Appendix B: Summary of Proposed Risk Mitigation for Hymexazol

Registration Review Case#: 7016
PC Code:129107
Hymexazol Type: fungicide
Hymexazol Family: isoxazole
Mode of Action: nucleic acid synthesis inhibitor

Affected Population(s)	Source of Exposure	Route of Exposure	Duration of Exposure	Potential Risk(s) of Concern	Proposed Mitigation
✓ Occupational handler (Mixers and Multiple Activities) ✓ Mammals ✓ Birds	✓ Mixing and multiple activities from treating seeds ✓ Planted treated seeds	✓ Inhalation and dermal exposure from the seed treatment process ✓ Consumption of hymexazol-treated seed	✓ Acute ✓ Sub-Chronic ✓ Chronic	✓ Short-term and intermediate ✓ Reproductive effects for birds and mammals (short and intermediate-term risks)	✓ Reduce application rate ✓ Add PPE

Appendix C: Hymexazol Label Table

Summary of Proposed Labeling Changes for Hymexazol Uses		
Description	Proposed Labeling Language for Hymexazol Use Products	Placement on Label
End Use Products		
Language to reduce maximum application rate	"Application as a standard pellet: Apply as a commercial seed treatment on pelleted sugar beet seeds at the rate of 45 grams or below of TACHIGAREN 70 WP per unit of 100,000 seeds (approx. 1 kilogram of raw sugar beet seed)."	Directions for Use
Language to reduce inhalation risks, require filtering face piece respirator (PF5 filter)	For **mixers**, remove current respirator language, and substitute: "Wear a minimum of a NIOSH approved filtering face piece respirator with any N, P or R filter (TC-84A). You can also use other NIOSH approved particulate respirators that offer more protection such as: • Half face respirator with any N, R, or P filter; (TC-84A) • Full Face respirator with any N, R, or P filter (TC-84A); or • Powered air purifying respirator with an HE filter (TC-21C) Drop the "N" type prefilter from the respirator statement, if the pesticide product contains, or is used with oil."	Precautionary Statements Under "Hazards to Humans and Domestic Animals"
Language to reduce inhalation risks, require a filtering face piece respirator (PF5 filter)	"**Respirator fit testing, medical qualification, and training** Using a program that conforms to OSHA's requirements (see 29 CFR Part 1910.134), employers must verify that any handler who uses a respirator is: • Fit-tested and fit-checked, • Trained, and • Examined by a qualified medical practitioner to ensure physical ability to safely wear the style of respirator to be worn. A qualified medical practitioner is a physician or other licensed health care professional who will evaluate the ability of a worker to wear a respirator. The initial evaluation consists of a questionnaire that asks about medical conditions (such as a heart condition) that would be problematic for respirator use. If concerns are identified, then additional evaluations, such as a physical exam, might be necessary. The initial evaluation must be done before respirator use begins. Handlers must be reexamined by a qualified medical practitioner if their health status or respirator style or use-conditions change. • Upon request by local/state/federal/tribal enforcement personnel, employers must provide documentation demonstrating how they have complied with these requirements."	Precautionary Statements Under "Hazards to Humans and Domestic Animals"
Compliance with the LRM	"The Federal Seed Act requires that bags containing seed treated with this product shall be labeled with the following information: "The seed has been treated with hymexazol. Do not use for food, feed or oil purposes"	Directions for Use

Compliance with the LRM	"Note: This product does not contain dye and is not covered by an appropriate tolerance, tolerance exemption, or other clearance under the Federal Food, Drug and Cosmetic Act. To comply with 40 CFR 153.155, therefore, all seed treated commercially with this product must be colored with an EPA-approved dye or colorant of a sutiable color to prevent accidental use as food for man or feed for animals."	Directions for Use
General Safe-Handling	"The U.S. EPA requires the following statements on containers containing seed treated with hymexazol: • Treated seeds exposed on soil surface may be hazardous to wildlife. Cover or collect treated seeds spilled during loading and planting. Treated seed must be incorporated into the soil • Dispose of all excess treated seed by burying seed away from bodies of water. • Do not contaminate water bodies when disposing of planting equipment wash waters. • Do not allow children, pets or livestock to have access to treated seeds. • Dispose of seed packaging or containers in accordance with local requirements."	Environmental Hazards