UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: March 8, 2022

SUBJECT: 9,10-Anthraquinone: Draft Human Health Risk Assessment for Registration Review.

PC Code: 122701
Decision No.: 577091
Petition No.: NA
Risk Assessment Type: Single chemical, aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D462810
Registration No.: See Use Profile Table
Regulatory Action: Registration Review
Case No.: 6054
CAS No.: 84-65-1
40 CFR: No tolerances

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As part of Registration Review, PRD of the Office of Pesticide Programs (OPP) has requested that HED evaluate the hazard and exposure data and conduct dietary, occupational, and residential exposure and aggregate risk assessments, as needed, to estimate the risk to human health that will result from the currently registered uses of 9,10-anthraquinone.

9,10-Anthraquinone was first registered by the Biopesticides and Pollution Prevention Division (BPPD) as a general avian repellent for seed treatment use on corn (Sections 3 and 24(c)) and rice (Section 18), and foliar use on turf (areas near airports, commercial sites, industrial office sites, municipal sites, developed urban areas, golf courses, sports fields, parks, home lawns,

cemeteries, landfills and dumpsters). In August 2015, OPP reclassified 9,10-anthraquinone as a conventional chemical.

This is the first draft risk assessment (DRA) for 9,10-anthraquinone as a conventional chemical. The toxicology endpoints, residue chemistry review, drinking water estimates and dietary, occupational, residential, and aggregate exposure assessments were updated according to current practices.

A summary of the findings and an assessment of human risk resulting from the registered uses of 9,10-anthraquinone are provided in this document.

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1.0 Executive Summary

9,10-Anthraquinone is currently undergoing registration review. It is used as a bird repellent on areas that may experience bird pressure, including turf (areas near airports, commercial sites, industrial office sites, municipal sites, developed urban areas, golf courses, sports fields, parks, home lawns, cemeteries, landfills, and dumpsters). Additionally, 9,10-anthraquinone is also registered for use as a liquid commercial seed treatment on field/sweet corn and rice (Section 3 registrations) and as a dust on-farm hopper box seed treatment on field/sweet corn (as Section 24(c) Special Local Needs (SLNs) registrations) for protection against consumption by birds.. It is currently not considered a food/feed use chemical for corn seed treatment use; however, the rice seed treatment use is a food/feed use. Three Section 3 registrations for 9,10-anthraquinone end-use products have been recently cancelled (EPA Reg. Nos. 69969-1, 69969-4; 86 FR 50116) or expired (EPA Reg. No. 69969-5, expired as of October 4, 2020). EPA Reg. Nos. 69969-1, 69969-4, and 69969-5 were a 50% ai turf product, a 50% ai liquid rice seed product, and a 50% ai liquid corn seed product, respectively. HED has not assessed the uses for these cancelled/expired end-use product registrations.

Use Profile
The Section 3 registered end-use products (EPA Reg. Nos. 69969-6 and 69969-7) assessed as part of registration review are formulated as liquids containing 13.6% to 18.6% ai. For turf uses, the maximum application rate is 1.03 lbs ai/A, or 0.172 lbs ai/gallon solution, and application equipment includes groundboom, backpack, manually pressurized handwand, and a mechanically pressurized handgun. For rice seed treatment, the maximum application rate is 0.0029 lbs ai/lbs rice seed. The field and sweet corn maximum application rate is 0.00165 lbs ai/lbs corn seed. The liquid seed treatment uses may only be used in commercial seed treatment equipment. Applicators are required to wear baseline attire plus chemical-resistant gloves and a NIOSH-approved respirator with a protection factor of 10 (PF10).

There are also multiple Section 24(c) SLN registrations of the dust seed treatment formulation, all containing 97.1% ai, for use on-farm on field and sweet corn. The maximum application rate is 0.00485 lbs ai/lb seed. Application equipment includes hopper box on-farm seed treatment equipment, and handlers must wear baseline attire plus chemical-resistant gloves and a PF10 respirator.

The restricted-entry interval (REI) on registered rice seed treatment and on-farm hopper box corn seed treatment labels is 4 hours. The registered labels for turf and commercial liquid corn seed treatment uses do not state an REI.

Pesticidal Exposure Profile
Anticipated exposures include dietary (food (rice) + drinking water), occupational handler (dermal and inhalation) for the seed treatment and turf uses, and occupational post-application (dermal only) for the turf uses. Residential exposures are expected from the registered turf uses. Residential post-application exposure assessments were conducted based on the registered turf uses including home lawns, golf courses, and parks. Dermal (adults and children) and incidental oral (children only) via residential post-application exposures from turf uses are anticipated. Exposure durations are expected to be both short- (1 to 30 days) and/or intermediate-term (1 to 6

months) for occupational handlers. Post-application worker and residential exposures are expected to be short-term (1 to 30 days) in duration.

Other Sources of 9,10-Anthraquinone

While monitoring data associated with the use of 9,10-anthraquinone as a pesticide are not available, global monitoring data from its other uses may be found in published scientific literature. It is noted that 9,10-anthraquinone is a High Production Volume (HPV) chemical that is used in industry (*e.g.*, to manufacture water insoluble dyes and in paper and pulp production) as well as emitted from diesel and gasoline engines (IARC, 2018). 9,10-Anthraquinone is produced by three different methods: oxidation of anthracene, Diels-Adler reaction between 1,4-naphthoquinone and 1,3-butadiene, and Friedel-Craft reaction between benzene and phthalic anhydride with further treatment with concentrated sulfuric acid (Butterworth et al., 2004). Because anthracene is generally obtained from distilling coal tar, 9,10-anthraquinone obtained from oxidation of anthracene can contain varying amounts of polycyclic aromatic hydrocarbons (PAHs) (Butterworth *et al*., 2004). 9,10-Anthraquinone may also be formed in the environment from combustion processes and from the degradation of other PAHs in the atmosphere. It is formed as a transformation product of the degradation of anthracene through photolysis and biodegradation (IARC, 2018). While 9,10-anthraquinone has been detected on a global basis in environmental media (groundwater, surface and tap water, soil, sediment, plants, fish and seafood tissue, animal tissue, precipitation, and air; IARC, 2018), the available global monitoring data cannot be specifically associated with its use as a pesticide. Given the lack of reliable current information and data to estimate residues of 9,10-anthraquinone from sources other than its pesticidal uses or even to determine the relative importance of those other sources, this risk assessment only addresses the pesticidal uses of 9,10-anthraquinone.

Hazard Characterization and Dose Response

The toxicological database for 9,10-anthraquinone is complete. Based on a weight-of-evidence (WOE) approach and considering all available 9,10-anthraquinone hazard and exposure information, the Hazard and Science Policy Council (HASPOC) recommended that the requirement for a subchronic inhalation study in rats, a 90-day repeated dose study in dogs, acute and subchronic neurotoxicity studies, a two-generation reproduction study, and a comparative thyroid toxicity study be waived. Repeated dosing of 9,10-anthraquinone affects the liver, kidney, and thyroid. Body weight decreases were also observed in both sexes of rats following subchronic oral exposure but only in female rats following chronic exposure. Throughout the 9,10-anthraquinone database, the dose response data seen for a majority of effects were non-linear; i.e., as doses increased over a very large range, the effect plateaued and there was generally no substantial increase in incidence and/or severity. Liver, kidney, and thyroid toxicity occurred in rats and mice following subchronic (via dietary and/or dermal) and/or chronic dietary exposures across a very large dose range. No increased quantitative sensitivity was seen in either the developmental rat or rabbit toxicity studies. Kidney tumors were seen in female F344 rats, and liver and thyroid tumors were seen in male and female mice. 9,10-Anthraquinone is classified as “Likely to be Carcinogenic to Humans” with a cancer slope factor (Q_1*), $(mg/kg/day)^{-1}$ of 6×10^{-2} in human equivalents of 9,10-anthraquinone.

9,10-Anthraquinone exhibits low acute toxicity by the oral, dermal, and inhalation routes. 9,10-Anthraquinone is minimally irritating for both eye and dermal irritation. It is not a dermal sensitizer.

No endpoint attributable to a single dose was identified, therefore, an acute dietary endpoint was not selected. The point of departure (POD) of 25 mg/kg/day (lowest-observed adverse-effect level (LOAEL)) selected from a chronic toxicity/carcinogenicity study in rats for the chronic dietary endpoint is based on decreased body weight in females, and kidney and liver effects in both sexes. The POD of 44 mg/kg/day (LOAEL) selected for incidental oral (children 1 to <2 years old), adult oral, and inhalation exposures is based on decreased body weight in females from a subchronic toxicity study in rats. No dermal hazard was identified in the route specific study and there was no evidence of increased quantitative sensitivity; therefore, a dermal endpoint was not selected.

The 10X Food Quality Protection Act (FQPA) Safety Factor (SF) is retained for all exposure scenarios as the studies selected to establish the chronic dietary POD and the occupational/ residential PODs did not identify a no-observed adverse-effect level (NOAEL). A total uncertainty factor (UF) of 1000X (10X to account for interspecies extrapolation, 10X for intra-species variation, and 10X FQPA SF in the form of a UF_L for LOAEL to NOAEL extrapolation) is applicable to these assessments.

Dietary Exposure Assessment
The residue chemistry and environmental fate databases for 9,10-anthraquinone are incomplete. HED and the Environmental Fate and Effects Division (EFED) have determined that, based on the available limited data, only residues of the parent compound, 9,10-anthraquinone, are included in this risk assessment as residues of concern in rice and drinking water. Due to the lack of data, there is uncertainty as to: (1) whether additional metabolites and/or degradates of 9,10-anthraquinone in rice commodities and/or drinking water are of concern for chronic and/or cancer dietary risk and (2) whether finite residues of concern for chronic and/or cancer dietary risk may be incurred in livestock (cattle (beef and dairy), swine, and poultry) commodities due to consumption of rice feed stuffs treated with 9,10-anthraquinone. HED notes that based on the available limited residue chemistry and environmental data, dietary exposure to residues of free 1-hydroxyanthraquinone or free 2-hydroxyanthraquinone (the only significant metabolites identified in the rat) from rice commodities and drinking water resulting from the registered uses of 9,10-anthraquinone assessed as part of registration review is expected to be negligible compared to the parent. [Note: Studies did not look for conjugates of 1-hydroxyanthraquinone or 2-hydroxyanthraquinone.] While there is the potential for other metabolites and/or degradates of 9,10-anthraquinone in rice and drinking water, it is uncertain as to whether any would be considered significant for chronic non-cancer dietary exposure or to have carcinogenic potential. In the absence of livestock metabolism or feeding study data, residues of 9,10-anthraquinone in livestock commodities were not included in this assessment. Additional residue chemistry and fate data are required to address uncertainties and confirm that only residues of parent are of concern in rice and drinking water and to confirm that there are no finite residues of concern in livestock commodities. It should be noted that submission of the additional data may also provide for refinements to the exposure estimates in future risk assessments.

An acute dietary endpoint was not selected; therefore, an acute dietary exposure assessment was not required. The chronic non-cancer dietary exposure assessment for residues of 9,10-anthraquinone (parent only) in rice commodities and drinking water is unrefined. The general U.S. population and all population subgroups use <1% of the chronic population-adjusted dose (cPAD). In addition to the inherent conservatism of using residue and fate data for dietary risk assessment, the following conservative inputs were incorporated into the assessment:

(1) Residues of 9,10-anthraquinone in/on rice commodities were estimated from field trial data and are based on the maximum residue of parent found in/on rice grain (0.05 ppm).
(2) Default processing factors were used for rice, brown (1.25x) and rice, flour (1.25x) and, in the absence of processing data, maximum theoretical concentration factors were used for rice, bran (7.7x) and rice, white (1.5x); hence, factors were used for all food forms of rice in the assessment.
(3) The analysis assumed 100% of the rice crop was treated.
(4) EFED provided a conservative 1-in-10-year annual average estimated drinking water concentration (EDWC) of 1.61 ppb for 9,10-anthraquinone for the chronic non-cancer dietary assessment.

The cancer dietary exposure assessment for residues of 9,10-anthraquinone (parent only) in rice commodities and drinking water is unrefined. It used the same inputs for residues of 9,10-anthraquinone in/on rice commodities as the chronic non-cancer dietary exposure assessment. EFED provided a conservative 30-year average EDWC of 1.26 ppb for 9,10-anthraquinone for the cancer dietary assessment. HED reports cancer risk for the adult population subgroup with the highest cancer risk estimate. For 9,10-anthraquinone, that subgroup is Adults 20-49, which has a cancer risk estimate of 3×10^{-6}; white rice and drinking water contributed 41% and 54%, respectively, to the total exposure estimate. The cancer risk estimate for residues of 9,10-anthraquinone (parent only) in rice commodities only is 1×10^{-6}.

Although there is some uncertainty in the dietary risk assessments due to incomplete residue chemistry and fate databases, the chronic non-cancer and cancer dietary assessments are not likely to underestimate dietary risks and an additional database uncertainty factor is not needed for this risk assessment. This is primarily due to (1) the number and magnitude of the conservative inputs that were incorporated into the risk assessments (discussed above), (2) the fact that the rice use is only seed treatment, and; therefore, residues in rice commodities are expected to be relatively low, and (3) the supporting qualitative evidence provided by the sweet corn radiotracer study that the anticipated residue estimate used in the dietary assessments for rice grain (0.05 ppm) is not likely to greatly underestimate the potential total residue exposure for rice grain in the dietary assessments. The following factors, in the order of importance, further support this position: (1) EFED has acknowledged that clarification on the turf use and the additional fate data that are being required may also result in lower EDWCs than those used in this risk assessment (C. Sutton, D462175, 3/07/2022) and (2) future refinements to the PCT assumption for rice used in this assessment (i.e., 100%) and the submission of rice processing data to refine anticipated residue estimates in white rice (i.e., the major food form contribution to the chronic non-cancer and cancer dietary assessments) and rice bran (i.e., the major potential feed form contribution to livestock dietary burdens) are expected to reduce exposure estimates

used in this risk assessment or the potential for exposure for residues of concern in rice and secondary residues in livestock commodities. However, it should be noted that the conservative inputs used in this assessment are deemed necessary to compensate for the uncertainties due to the lack of data; hence, no refinements to the exposure estimates for rice commodities can be undertaken until residue chemistry data deficiencies (see Section 2.1 Data Deficiencies for details) are satisfied and uncertainties due to the incomplete residue chemistry database are adequately addressed.

Residential Exposure and Risk Assessment
There are registered turf uses of 9,10-anthraquinone that are expected to result in residential exposures. The registered 9,10-anthraquinone product label (EPA Reg. No. 69969-7) with residential use sites (e.g., lawn, parks, sports fields, and golf course turf) requires that handlers wear specific clothing (e.g., long-sleeve shirt/long pants) and/or use personal protective equipment (PPE). Therefore, HED has made the assumption that this product is not for homeowner use, and has not conducted a residential handler assessment.

Residential post-application exposure assessments were conducted based on the registered turf uses including to home lawns, golf courses, and parks. All residential post-application non-cancer incidental oral exposures resulted in no risk estimates of concern (i.e., margins of exposure (MOEs) ≥ the level of concern (LOC); LOC=1,000) for children (1 to <2 years old) with MOEs ranging from 2,200 to 1,300,000 using chemical-specific transferable turf residue (TTR) data.

Although a non-cancer dermal risk assessment was not performed because a non-cancer dermal endpoint was not selected, a dermal post-application cancer exposure and risk assessment was performed for adults because dermal exposure contributes to the overall cancer risk for 9,10-anthraquinone. Residential post-application cancer risk estimates for registered turf uses of 9,10-anthraquinone range from 2×10^{-4} to 5×10^{-7}, depending on activity (e.g., high contact lawn activities, mowing, or golfing).

Aggregate Risk Assessment
In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. There is no applicable endpoint attributable to a single dose, so there is no acute POD and acute dietary and aggregate risk assessments are not required. There are no residential long-term exposures expected based on the registered use pattern; therefore, the chronic aggregate risk estimates are equivalent to the chronic non-cancer dietary estimates.

In aggregating short-term risk, the Agency routinely combines background chronic dietary (rice + drinking water) exposure with short-term residential exposures. Using the post application exposures for children 1 to <2 years old via incidental oral exposure from high contact activities on treated turf, combined with the applicable subpopulation dietary exposures, there was no short-term residential non-cancer aggregate risk estimate of concern. The short-term aggregate non-cancer margin of exposure (MOE) was 2,200 and is not a risk estimate of concern (level of concern (LOC) ≤ 1,000).

For the cancer aggregate assessment, the recommended residential exposure is dermal exposure to adults from post-application exposure to turf. The cancer aggregate risk is calculated using a cancer slope factor (Q_1*) of 6 x 10^{-2} $(mg/kg/day)^{-1}$ multiplied by the sum of the residential (high contact lawn activities) and dietary exposure (for adults 20-49 years old, the most highly exposed adult population subgroup) estimates. The cancer aggregate risk estimate is 2 x 10^{-4}.

Non-Occupational Spray Drift Assessment
One 9,10-anthraquinone product label is registered for use on turf (i.e., home lawns), thus it was considered whether the risk assessment for that use may be protective of any type of exposure that would be associated with spray drift. Since the maximum application rate on non-residential lawn turfgrass (i.e., parks, sports fields, and golf courses) adjusted by the amount of drift expected is less than or equal to existing residential lawn turf application rates, the existing turf assessment is considered protective of spray drift exposure and does not result in non-cancer risk estimates of concern. Therefore, a quantitative spray drift assessment for 9,10-anthraquinone is not required and was not conducted.

Occupational Handler Exposure
Based on the anticipated use patterns and current labeling, types of equipment, and techniques that can potentially be used, occupational handler exposure is expected from the registered uses. Occupational handler non-cancer risk estimates are based on inhalation exposure and are not of concern (i.e., MOEs ≥LOC; LOC = 1,000) at label-required PPE (i.e., protection factor 10 (PF10) respirator) with MOEs ranging from 1,100 to 3,100,000.

Although a non-cancer dermal risk assessment was not performed because a non-cancer dermal endpoint was not selected, a dermal cancer exposure and risk assessment was performed because dermal exposure contributes to the overall cancer risk for 9,10-anthraquinone. Occupational handler cancer risk estimates range from 9 x 10^{-5} to 5 x 10^{-8} for private handlers (a grower or worker that applies pesticides to land owned or operated by the grower) and 2 x 10^{-4} to 1 x 10^{-7} for commercial handlers (applicators that complete multiple applications for multiple clients) of various PPE combinations including utilizing seed treatment equipment while operators wear gloves and respirators.

Occupational Post-Application Exposure
Occupational post-application dermal exposure is anticipated from registered 9,10-anthraquinone turfgrass uses; however, a non-cancer dermal endpoint was not selected. Therefore, occupational post-application non-cancer dermal exposures have not been quantitatively assessed.

Although a non-cancer dermal risk assessment was not performed, a dermal cancer exposure and risk assessment was performed because dermal exposure contributes to the overall cancer risk for 9,10-anthraquinone. Occupational post-application cancer risk estimates to occupational workers performing maintenance activities on golf course turfgrass previously treated with 9,10-anthraquinone range from 5 x 10^{-6} to 3 x 10^{-6}.

Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for 9,10-anthraquinone at this time. If new

policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for 9,10-anthraquinone.

Environmental Justice
Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations."

Human Studies
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their exposure. Appendix C provides additional information on the review of human research used to complete the risk assessment. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied (see Appendix C).

2.0 Risk Assessment Conclusions

HED has examined the toxicology, residue chemistry, and exposure data to estimate the risk to human health that will result from the proposed uses of 9,10-anthraquinone. Overall conclusions regarding risks are summarized below.

The seed treatment use of 9,10-anthraquinone on rice is considered a food/feed use (B. Cropp-Kohlligian, D461484, 6/03/2021; ChemSAC meeting 5/26/2021). This is the only registered food/feed use for 9,10-anthraquinone. At this time, no tolerances for residues of 9,10-anthraquinone have been established. The additional data summarized in Section 2.1 below are required before HED can determine the tolerance definition(s)/commodities/level(s) for 9,10-anthraquinone residues of concern that need to be established to cover the rice seed treatment use. HED does not have the discretion to recommend for the establishment of tolerances until all residue chemistry data required under Part 158 of the CFR are satisfied.

Although there is some uncertainty in the dietary risk assessments due to incomplete residue chemistry and fate databases, the chronic non-cancer and cancer dietary assessments are not likely to underestimate dietary risks given the number and magnitude of conservative inputs that were incorporated into the assessments. However, it should be noted that no refinements to the conservative inputs for rice commodities can be undertaken until residue chemistry data deficiencies are satisfied and uncertainties due to the incomplete residue chemistry database are adequately addressed.

There were no risks of concern identified in the non-cancer chronic dietary, residential, aggregate, and occupational assessments at the label required PPE (i.e., respirators).

The unrefined dietary cancer risk for adults is estimated at 3×10^{-6}. Residential post-application cancer risk estimates for registered turf uses of 9,10-anthraquinone range from 2×10^{-4} to 5×10^{-7} . Occupational handler cancer risk estimates range from 9×10^{-5} to 5×10^{-8} for private handlers and 2×10^{-4} to 1×10^{-7} for commercial handlers of various PPE combinations including

utilizing seed treatment equipment while operators wear gloves and respirators. Occupational post-application cancer risk estimates to occupational workers performing maintenance activities on golf course turfgrass previously treated with 9,10-anthraquinone range from 5×10^{-6} to 3×10^{-6}. The cancer aggregate risk estimate is 2×10^{-4} for the most highly exposed adult population subgroup (20-49 years old) from post-application exposure to turf.

2.1 Data Deficiencies

Residue Chemistry: All of the data listed below are required under Part 158 of the 40 CFR in order to establish tolerances for residues resulting from the seed treatment use of 9,10-anthraquinone on rice. Pending the outcome of these studies, additional data may be needed.

- OCSPP Guideline 860.1300 Nature of the Residue – Plants, Livestock.
  Plant metabolism data are required for rice tolerances given that the currently registered use on rice is considered a food/feed use. [Note: While a rice metabolism study is expected to elucidate the nature of the residue in rice from the registered seed treatment use of 9,10-anthraquinone on rice for regulation and risk assessment purposes, it would not induce HED to rescind the food/feed determination for rice.] Livestock metabolism data are required to address whether livestock tolerances are needed given that rice commodities are livestock feed stuffs for cattle (beef and dairy), swine, and poultry.
  Note: HED has conducted a dietary risk assessment without these data using the following assumptions: (1) only parent, 9,10-anthraquinone, is a residue of concern in/on rice and (2) no finite residues of concern were incurred in livestock (cattle (beef and dairy), swine, and poultry) commodities due to consumption of rice feed stuffs treated with 9,10-anthraquinone to the extent that tolerances are needed for livestock commodities. To compensate for the lack of these data, conservative inputs were incorporated into the dietary exposure/risk assessments. Once submitted, these data may change the qualitative characteristics of the dietary exposure/risk; however, given the number and magnitude of the conservative inputs incorporated into the quantitative dietary exposure assessments, they are not expected to result in a significant increase in the magnitude of the dietary exposures. This is based on the understanding that, when the outstanding data are submitted and address the uncertainties due to the lack of data, that the conservative inputs, that are currently needed, may be altered to refine future dietary assessments. In the meantime, the dietary exposures/risks for rice cannot be refined until the residue data deficiencies are addressed.
- OCSPP Guideline 860.1340 Residue Analytical Method.
  A residue analytical method suitable for enforcement purposes is required whenever a numeric tolerance is proposed.
- OCSPP Guideline 860.1360 Multiresidue Methods.
  Data are required to determine whether FDA/USDA multiresidue methodology would detect and identify the pesticides and any metabolites.
- OCSPP Guideline 860.1380 Storage Stability.
  Adequate supporting storage stability data are required for the studies listed here.
- OCSPP Guideline 860.1520 Processed Food/Feed.
  A rice processing study is required.
  Note: HED has conducted a dietary risk assessment without these data. To compensate

for the lack of these data, maximum theoretical concentration factors were used for rice, bran (7.7x) and rice, white (1.5x).

- OCSPP Guideline 860.1850 Confined Accumulation in Rotational Crop
  Required when the Agency determines that it is reasonably foreseeable that a food or feed crop could be subsequently planted on the site of pesticide application after harvest or failure of the treated crop.
  Note: Alternatively, for the currently registered uses of 9,10-anthraquinone as a seed treatment on corn and rice only, these data are not required if all 9,10-anthraquinone labels registered for use on crops restrict rotation to only those crops for which 9,10-anthraquinone is already registered for use and specify a 365-day plantback interval (PBI) for all other crops. This option is not automatically applicable to any future uses of 9,10-anthraquinone. HED has conducted a dietary risk assessment without these data and assumed, with adequate PBIs on labels, that there will be no 9,10-anthraquinone residues of concern in rotated crops. Hence, until this data requirement is addressed, a 365-day PBI for all crops other than corn (field and sweet) is the adequate PBI and should be specified on 9,10-anthraquinone labels registered for use on crops.

Toxicology: None

Occupational/Residential Exposure: None

2.2 Tolerance Considerations

The seed treatment uses of 9,10-anthraquinone on corn (field and sweet) are considered nonfood/nonfeed (B. Cropp-Kohlligian, D459655, 3/17/2021); however, the seed treatment use of 9,10-anthraquinone on rice is considered a food/feed use (B. Cropp-Kohlligian, D461484, 6/03/2021; HED Chemistry Science Advisory Council (ChemSAC) meeting 5/26/2021). At this time, no tolerances for residues of 9,10-anthraquinone have been established. The additional data summarized in Section 2.1 above are required before tolerances for residues of 9,10-anthraquinone can be established. No Codex, Canadian, or Mexican maximum residue limits (MRLs) for residues of 9,10-anthraquinone have been established at this time.

2.3 Label Recommendations

2.3.1 Recommendations from Residue Reviews

No rotational crop data are available for 9,10-anthraquinone. Taken together, the available data indicate that residues of 9,10-anthraquinone may be readily taken up by plants from 9,10-anthraquinone treated seed (B. Cropp-Kohlligian, D461484, 6/03/2021). Hence, the potential for residues of 9,10-anthraquinone to be taken up by rotated crops cannot be dismissed. Therefore, pending submission of the required confined accumulation in rotational crop data (OCSPP Guideline 860.1850), all 9,10-anthraquinone labels registered for use on crops should be revised to restrict rotation to only those crops for which 9,10-anthraquinone is already registered for use (corn (field and sweet) and rice). A 365-day PBI should be imposed for all other crops. Labels should include language similar to the following, “Do not rotate to crops other than corn and rice for a period of one year.”

2.3.2 Recommendations from Residential Assessment

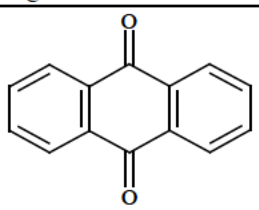
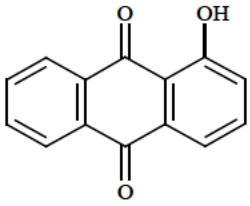
None.

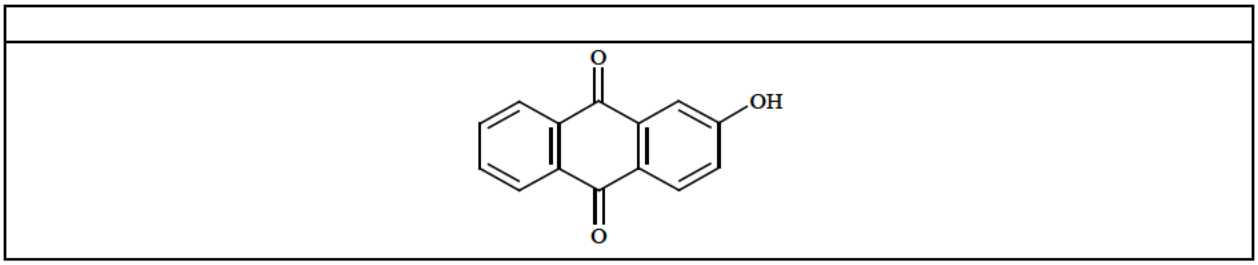
2.3.3 Recommendations from Occupational Assessment

HED is recommending that the REI be revised on the applicable registered labels, which currently require a 4 hr REI, since the criteria for a reduced REI in Pesticide Registration (PR) Notice 95-3 is not met. HED recommends a 12 hr REI. In addition, conflicting post-application label statements on product 69969-7 related to workers entering flooded fields should be reviewed. Further information is provided in Section 11.2.1.

3.0 Introduction

3.1 Chemical Identity

Table 3.1.1 Nomenclature for 9,10-Anthraquinone and Metabolites of Interest.	
Common name	Anthraquinone
Identity	9,10-anthracenedione
CAS registry number	84-65-1
Molecular weight	208.21 g/mol
	
Metabolite name	1-hydroxyanthraquinone
Identity	1-hydroxyanthraquinone
CAS registry number	129-43-1
Molecular weight	224.22 g/mol
Other synonyms	1-OH-anthraquinone
	
Metabolite name	2-hydroxyanthraquinone
Identity	2-hydroxyanthraquinone
CAS registry number	605-32-3
Molecular weight	224.22 g/mol
Other synonyms	2-OH-anthraquinone



3.2 Physical/Chemical Characteristics

9,10-Anthraquinone appears as yellow crystals or powder. It has an estimated vapor pressure of 1.16×10^{-7} mmHg making volatilization an unlikely route of dissipation. It has an octanol/water partition coefficient of log Kow = 3.39 at pH 7 indicating that it is more fat soluble than water soluble, exhibiting a tendency to dissolve in fats, oils, lipids, and non-polar solvents more readily than in water. It is only moderately soluble in water (1.75 mg/L at 25°C; see Food and Agriculture Organization (FAO) water solubility classification). More detailed physicochemical properties of 9,10-anthraquinone are summarized in Appendix B.

3.3 Pesticide Use Pattern

9,10-Anthraquinone is used as a bird repellent, applied to areas that may experience bird pressure, including turf (areas near airports, commercial sites, industrial office sites, municipal sites, developed urban areas, golf courses, sports fields, parks, home lawns, cemeteries, landfills, and dumpsters). Additionally, 9,10-anthraquinone is also registered for use as a liquid commercial seed treatment on field/sweet corn and rice and as a dust on-farm hopper box seed treatment on field/sweet corn (as SLNs) for protection against consumption by birds.

In 1998, 9,10-anthraquinone was first registered by BPPD as a general avian repellent for seed treatment use on corn and rice, and foliar use on turf including commercial and industrial grounds, golf courses, rooftops, and other non-food terrestrial areas. Two new registrations for use on corn and rice seed contain significantly lower percent 9,10-anthraquinone (results in reduced application rates). According to the registrant, they do not intend to continue supporting the existing higher percent ai registrations. Registrations EPA Reg. Nos. 69969-1 and 69969-4 (50% ai turf product and 50% ai liquid rice seed product, respectively) have been cancelled and have not been quantitatively assessed here, and they have been replaced by EPA Reg. No. 69969-7 (18.6 % ai), resulting in a reduced application rate to both turf and rice seed use sites.

The currently registered turf use label (EPA Reg. No. 69969-7) is formulated as a liquid product and contains 18.6% ai. For turf uses, the maximum application rate is 1.03 lbs ai/A or 0.172 lbs ai/gallon solution. It can be applied up to 7 times per year at a 14 to 21-day re-treatment interval. It can be applied via groundboom, backpack, manually pressurized handwand, and a mechanically pressurized handgun. Applicators are required to wear baseline attire plus chemical-resistant gloves and a PF10 respirator.

The liquid turf label referenced above also contains a commercial seed treatment use of rice. For rice seed treatment, the maximum application rate is 0.0029 lbs ai/lbs rice seed. One application per year is allowed with no more than 0.44 lbs ai/A/year. It can only be used in commercial seed treatment equipment and handlers must wear baseline attire, chemical-resistant gloves, goggles, and a PF10 respirator.

The currently registered field and sweet corn seed treatment use label (EPA Reg. No. 69969-6) is formulated as a liquid product and contains 13.6% ai. The field and sweet corn maximum application rate is 0.00165 lbs ai/lbs corn seed with a maximum of 0.05 lbs ai/A/year. It can only be used in commercial seed treatment equipment and handlers must wear baseline attire, chemical-resistant gloves, goggles, and a PF10 respirator.

There are also multiple Section 24(c) SLN registrations of a dust seed treatment formulation, all containing 97.1% ai, for use on-farm on field and sweet corn. The maximum application rate is 0.00485 lbs ai/lbs seed with no more than 1 application per acre per season. It can be used only in hopper box on-farm seed treatment equipment and handlers must wear baseline attire plus chemical-resistant gloves and a PF10 respirator.

The REI on registered rice seed treatment and on-farm hopper box seed treatment labels is 4 hours. The registered labels for turf and corn seed treatment uses do not state an REI.

The maximum single application rates of the registered uses of 9,10-anthraquinone and a summary of use directions are detailed in Table 3.3. below.

Table 3.3. Summary of Directions for Registered Uses of 9,10-Anthraquinone.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Max. Applic. Rate	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lbs ai/A)	Use Directions and Limitations
Turf (areas near airports, commercial sites, industrial office sites, municipal sites, developed urban areas, golf courses, sports fields, parks, home lawns, cemeteries, landfills, and dumpsters)					
Liquid (groundboom, backpack, manually pressurized handwand, mechanically pressurized handgun)	69969-7 AV-5055 (18.6% ai, 2.06 lbs ai/gallon product)	1.03 lbs ai/A (0.5 qts product with 1.5-5 gal water per 0.25 acre) 0.172 lbs ai/gal	Do not apply more than 7 times per year per area	7.21	Do not apply using a backpack sprayer in CA. PPE: Handlers must wear baseline attire, chemical resistant gloves, goggles, and PF10 respirator. Do not apply to sidewalks, parking lots, patios, etc. Dilute with 6-20 gallons of water per acre Spray with a medium-fine to fine droplet.

Table 3.3. Summary of Directions for Registered Uses of 9,10-Anthraquinone.					
Applic. Timing, Type, and Equip.	**Formulation [EPA Reg. No.]**	**Max. Applic. Rate**	**Max. No. Applic. per Season**	**Max. Seasonal Applic. Rate (lbs ai/A)**	**Use Directions and Limitations**
					Subsequent applications may be made at 14-21 day intervals or as required by geese activity/ anticipated seasonal migrations
Field and Sweet Corn Seed Treatment					
Liquid seed treatment with commercial seed treatment equipment	69969-6 AVIPEL Liquid Corn Seed Treatment (13.6% ai, 1.56 lbs ai/gallon product)	0.00165 lbs ai/lbs corn seed (product 13.5 fl oz/100 lbs corn seed); $1.2x10^{-6}$ lb ai/field corn seed; $9.2x10^{-7}$ lb ai/sweet corn seed	NA	0.05 lbs ai/A/year as a seed treatment	Use only in commercial seed treatment equipment. PPE: Handlers must wear baseline attire plus chemical-resistant gloves, goggles, and PF10 respirator. Handlers of treated seed must wear baseline attire and chemical-resistant gloves.
Rice Seed Treatment					
Liquid seed treatment with commercial seed treatment equipment	69969-7 AV-5055 (18.6% ai, 2.06 lbs ai/gallon product)	0.0029 lbs ai/lbs rice seed (18.3 fl oz product/100 lbs of rice seed); $1.9x10^{-7}$ lb ai/seed	NA	Do not apply more than 0.44 lbs ai/A/yr, 1 application allowed per acre per season.	Use only in commercial seed treatment equipment. Handlers must wear baseline attire, chemical-resistant gloves, goggles, and PF10 respirator. Do not allow workers to enter the rice paddy for 48 hrs after fields water-seeded with 9,10-anthraquinone treated seeds. PPE: Handlers of treated seed must wear baseline attire and chemical-resistant gloves. REI=4 hr (exception for soil-incorporated/ soil-injection). Do not drain water from AQ -treated rice fields to irrigate other crops, use for livestock or discharge into potable water sources. Do not allow children, pets, or livestock to have access to treated seed.

Table 3.3. Summary of Directions for Registered Uses of 9,10-Anthraquinone.					
Applic. Timing, Type, and Equip.	**Formulation [EPA Reg. No.]**	**Max. Applic. Rate**	**Max. No. Applic. per Season**	**Max. Seasonal Applic. Rate (lbs ai/A)**	**Use Directions and Limitations**
					Treated seed must not be used for or mixed with food or animal feed or processed for other uses.
SLNs Field and Sweet Corn					
Hopper box dry seed treatment	Multiple Reg. Nos. Avipel Hopper Box (dry) Corn Seed Treatment (97.1% ai)	0.00485 lbs ai/lbs seed (1.94 oz ai/25 lbs seed; 2.0 oz product/25 lbs seed); $3.6x10^{-6}$ lb ai/field corn seed; $2.7x10^{-6}$ lb ai/sweet corn seed	No more than 1 application per acre per season	NS	Use as a dry mixture in the planter box as a seed treatment just prior to planting. PPE: Baseline attire, chemical-resistant gloves, PF10 respirator, goggles. REI=4 hours

REI = re-entry interval. PPE = personal protective equipment. NA = not applicable. NS = not specified.

3.4 Anticipated Exposure Pathways

Humans may be exposed to 9,10-anthraquinone in food and drinking water. Residential exposures are expected from the registered uses of 9,10-anthraquinone. Non-occupational exposure to 9,10-anthraquinone via spray drift is possible. There is the potential for residential post-application exposures for both adults (dermal only) and children (dermal and incidental oral) from contact with previously treated turf. Occupational handler (dermal and inhalation) exposures are expected from the seed treatment and turf uses as well as occupational post-application (dermal only) exposures from the turf uses. This risk assessment considers the relevant exposure pathways based on all of the existing uses of 9,10-anthraquinone.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a

pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Spray drift can also potentially result in post-application exposure and it was considered in this analysis. Further considerations are also currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

4.1 Toxicology Studies Available for Analysis

The toxicology database for 9,10-anthraquinone is complete at this time. In December 2018, based on a WOE approach, considering all the available hazard and exposure data for 9,10-anthraquinone, the HASPOC recommended that the subchronic inhalation study in rats and the 90-day repeated dose study in dogs for 9,10-anthraquinone be waived, while recommending to require neurotoxicity and two-generation reproduction studies at that time (K. Yozzo, TXR 0057823, 1/29/2019). Subsequently, the HASPOC reconsidered the need for these studies following the receipt of additional information from the registrant. Taking this new information into consideration, the HASPOC met on October 15, 2020 and recommended that the acute and subchronic neurotoxicity studies and the two-generation reproduction study for anthraquinone also be waived at this time (M. Zampariello, TXR 0058067, 1/12/2021). Since thyroid effects were noted in the database, the HASPOC met again on July 22, 2021 to evaluate the need for a comparative thyroid assay. HASPOC recommended, based on the WOE, that this study also be waived (H. DeLeon, TXR 0058198, 7/29/2021). The 9,10-anthraquinone database contains the following studies, with the majority as part of a larger National Toxicology Program (NTP) study:

- Subchronic oral (dietary) toxicity in rats and mice
- Subchronic dermal toxicity in rats
- Developmental (gavage) toxicity in rats and rabbits
- Carcinogenicity (dietary) studies in rats and mice
- 28-day immunotoxicity (dietary) study in mice
- Mutagenicity battery
- Metabolism in rats
- Acute 6-pack studies

As part of registration review for 9,10-anthraquinone, a broad survey of the literature was conducted to identify studies that report toxicity following exposure to 9,10-anthraquinone via exposure routes relevant to human health pesticide risk assessment not accounted for in the Agency's 9,10-anthraquinone toxicology database. The search strategy employed terms restricted to the name of the chemical plus any common synonyms, and common mammalian models to capture as broad a list of publications as possible for the chemical of interest. The

search strategy returned 982 animal studies from the literature. During title/abstract and/or full text screening of these studies, four were identified as containing potentially relevant information (either quantitative or qualitative) for the 9,10-anthraquinone human health risk assessment. Following a more in-depth screen of the identified relevant studies, it was determined that these studies do not contain information that would impact the risk assessment and were not considered in the selection of endpoints or PODs. Refer to Appendix A.3 for additional information.

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

After oral exposure, 9,10-anthraquinone is slowly and incompletely absorbed, slowly distributed to tissues by a diffusion-limited transport process, and slowly metabolized and excreted via a saturable kinetic process. There is not a first-pass effect in the liver, as absorption appears to occur directly into venous blood. However, there is some evidence of enterohepatic cycling. Tissue concentrations in female rats are higher due to slow clearance and slower metabolism.

Plasma concentration-time curves for rats and mice following a single oral gavage dose were characteristic of first-order absorption and elimination, with a slow linear elimination phase. In rats, the plasma maximum concentration (C_{max}) increased proportionately in a dose-dependent manner (0.25-3.08 µg/mL). The time to reach this concentration (T_{max}) and area under the curve (AUC) also increased in a dose-dependent manner for male and female rats, at 8-18 hours and 3.54-51.2 µg/mL•min, respectively. The plasma half-life ($t_{1/2}$) for rats was estimated to be 12 hours at the lowest dose of 40 mg/kg and could not be determined at the two higher doses of 100 and 400 mg/kg. There were no appreciable differences between sexes in any parameter for rats. In mice, the C_{max} and AUC also increased in a dose-dependent manner and was proportional up to 200 mg/kg (0.68-2.11 µg/mL for C_{max} and 3.37-9.98 µg/mL•min for AUC); this proportional increase was not seen at the highest dose of 800 mg/kg for either C_{max} (3.47 µg/mL) or the AUC (21.9 µg/mL/min). The observed T_{max} for all groups of mice was 4 hours, while the observed $t_{1/2}$ was 4-6 hours. Experiments in which rats and mice received a single intravenous (IV) dose (2 or 4 mg/kg, respectively) showed that plasma concentration-time curves were biphasic in both species and sexes, indicating an initial tissue distribution phase followed by an elimination phase. In rats, the C_{max} did not differ between sexes (2.9-3.3 µg/mL), and the T_{max} was 2 minutes for both sexes. The estimated $t_{1/2}$ was 10-12 hours, while the AUC was estimated at 1.10-1.29 µg/mL•min. In mice, the T_{max} for both sexes was also 2 minutes. The C_{max} was slightly lower for males (2.7 and 3.4 µg/mL, respectively), while the AUC was slightly higher (3.45 and 2.16 µg/mL/min, respectively).

The metabolism and disposition of 9,10-anthraquinone in the male F344/N rat was also examined. Animals were administered radiolabeled-9,10-anthraquinone by intravenous (iv) injection of 0.35 mg/kg or by oral gavage at doses of 0.35 to 350 mg/kg. Results indicate that 9,10-anthraquinone was absorbed from the gastrointestinal tract and distributed to many tissues at low levels ranging from <0.01% to ~1% of dose. The highest concentration of 9,10-anthraquinone was initially found in the liver (≤1% of dose) and fat (≤0.5%). However, by 96 hours less than ~4% of the administered dose remained in major tissues, and no indication of bioaccumulation was apparent in any tissue. The majority of the radiolabeled 9,10-anthraquinone was eliminated in the feces (52-63%) and the urine (26-41%) by 96 hours after dosing for all

concentrations. Biliary excretion was confirmed by administering 9,10-anthraquinone to bile-duct cannulated rats. During the 6-hour period of sample collection, 35% of the administered dose was recovered in bile. Analysis of the bile samples showed that less than 3% of the radioactivity collected was present as the parent compound, suggesting extensive hepatic metabolism. Analysis of urine samples revealed the presence of as many as 11 metabolites. Two of the rat metabolites identified were 1-hydroxyanthraquinone and 2-hydroxyanthraquinone. Both of the hydroxylated metabolites have similar structures as the parent compound, so are assumed to have equal toxicity.

4.2.1 Dermal Absorption

In vivo and/or *in vitro* dermal absorption studies are not available for 9,10-anthraquinone. Therefore, a conservative dermal absorption factor (DAF) was estimated based on the ratio of the oral LOAEL (44 mg/kg/day) from the 90-day oral rat study (MRID 48708301) based on body weight decreases and the dermal NOAEL for body weight (1000 mg/kg/day) from the 28-day dermal rat study (MRID 48639801) which evaluated body weight decreases but showed no body weight decreases up to 1000 mg/kg/day. A DAF of 4% (44/1000 x100% = 4%) will be used to extrapolate oral doses to dermal equivalent doses when necessary.

4.3 Toxicological Effects

Repeated dosing of 9,10-anthraquinone affects the liver, kidney, and thyroid in rats and mice. Body weight decreases were also observed in both sexes of rats following subchronic oral exposure but only in female rats following chronic exposure. Throughout the 9,10-anthraquinone database, the dose response data seen for a majority of effects were non-linear; i.e., as doses increased over a very large range, the effect plateaued and there was generally no great increase in incidence and/or severity. This could be explained by the ADME data which showed that after oral exposure, 9,10-anthraquinone is slowly and incompletely absorbed, slowly distributed to tissues by a diffusion-limited transport process, and slowly metabolized, indicating that it remains readily bioavailable regardless of dose.

Liver toxicity occurred in rats (liver necrosis, vacuolation, cystic degeneration, inflammation, and eosinophilic and mixed-cell foci) and mice (increased liver weights and centrilobular hypertrophy, hepatocyte erythrophagocytosis, focal necrosis, fatty focal degeneration, and eosinophilic focus) following both subchronic (via dietary and/or dermal) and chronic (dietary) exposures across a very large dose range. Liver tumors were also seen in male and female mice following chronic exposure.

Following dietary and dermal exposures in rats and mice, observed hematology changes (decreased hemoglobin, hematocrit, and erythrocyte counts) and histopathological effects in the bone marrow and spleen were considered to be compensatory and not adverse due to a slight/minimal severity and lack of progression.

The kidney was a target in both male and female rats. Following subchronic exposure in female Sprague Dawley rats, the suite of adverse kidney effects included increased kidney weight, clinical chemistry changes in glucose, cholesterol and triglyceride, and kidney histopathology

(basophilia of the cortical tubules, pigment deposition in cortical tubules) which occurred at a relatively high dose (661 mg/kg/day). In F344 female rats, subchronic exposures resulted in increased urinary N-acetyl-β-D-glucosaminidase (NAG) enzyme activity in females. The urinary NAG provides early indication of tubular dysfunction resulting from nephrotoxic damage (Price, RG., 1992)[1]. NAG activity occurs prior to and is protective of the hyaline droplet accumulation and nephropathy seen at higher doses. Following chronic exposures in female F344 rats, kidney toxicity included renal tubular hyperplasia, mineralization of medulla, and pigmentation, as well as renal tubule tumors. Similar effects were seen in male rats following subchronic (increased kidney weights, basophilia of the cortical tubules, cortical tubules with hyaline droplets, hyaline droplet accumulation and nephropathy) and chronic exposure (hyaline droplet accumulation, nephropathy, pigmentation, renal tubule hyperplasia, and hyperplasia of transitional epithelium). Hyaline droplet formation may be associated with accumulation of $\alpha_{2\mu}$-globulin, which is a male rat specific phenomenon, and is not considered relevant to humans. Although $\alpha_{2\mu}$-globulin staining was measured in both sexes in the NTP study, $\alpha_{2\mu}$-globulin does not explain all kidney toxicity seen in male rats since similar effects were also seen in female rats. Therefore, it was determined that the etiology of the kidney toxicity in males cannot be attributed solely to $\alpha_{2\mu}$-globulin; another mechanism may also be occurring. In most studies, the adversity decisions related to the kidney effects are made only for the females, and not the males, due to this uncertainty. In the carcinogenicity study in rats, the kidney mineralization in males was considered to be adverse since this effect is not a typical effect that is seen with the $\alpha_{2\mu}$-globulin suite of effects. No adverse kidney effects were seen in the subchronic dermal study in rats.

There were no adverse kidney effects observed in mice. Following subchronic exposure in mice, adverse urinary bladder effects (cytoplasmic alteration of the transitional epithelial cells) of moderate severity or greater were seen in males and females; however, no adverse bladder effects were seen following chronic exposure.

Following both subchronic (oral and dermal) and chronic exposures in rats, thyroid toxicity was observed and included increased thyroid weights and thyroid follicular cell hypertrophy. Following chronic exposure in mice, thyroid toxicity included thyroid follicular cell hyperplasia as well as thyroid follicular cell tumors in both sexes. The thyroid effects were consistent across the database with the severity of the effects ranging from minimal to moderate and were considered to be adverse. Thyroid hormones were not measured.

No increased sensitivity was seen in either the developmental rat or rabbit toxicity studies. In the developmental rabbit toxicity study, maternal toxicity included increased mortality, late abortions (occurring on gestation days 25 and 28), and clinical signs. The late abortions were considered both a maternal and developmental effect. No additional developmental toxicity was seen in rabbits. In the developmental rat toxicity study, maternal effects (decreased body weight and food consumption) occurred at the same dose as the developmental effects (decreased fetal, litter and placental weights).

[1] Price RG. The role of NAG (N-acetyl-beta-D-glucosaminidase) in the diagnosis of kidney disease including the monitoring of nephrotoxicity. Clin Nephrol. 1992;38 Suppl 1:S14-9.

An immunotoxicity study in rats did not indicate that the immune system is a target for 9,10-anthraquinone toxicity. There was no evidence of neurotoxicity in the available toxicity database for 9,10-anthraquinone, which included a subchronic toxicity study in rats that evaluated neurological parameters (physical examination, arena observations, sensory reactivity, grip strength, and motor activity), as well as neurohistopathology.

9,10-Anthraquinone has low acute toxicity by the oral, dermal, and inhalation routes (Tox category IV). 9,10-Anthraquinone is minimally irritating (Toxicity Category IV) for both eye and dermal irritation. It is not a dermal sensitizer.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)[2]

The FQPA SF of 10X (in the form of a UF_L to account for LOAEL to NOAEL extrapolation) is retained for 9,10-anthraquinone. The 9,10-anthraquinone toxicology database is considered complete and adequate for risk assessment. The HASPOC considered waivers for a subchronic inhalation study, a 90-day dog study, acute and subchronic neurotoxicity studies, a two-generation reproduction study, and a comparative thyroid assay and recommended that these studies be waived (see section 4.1 for details). No prenatal susceptibility was seen in developmental toxicity studies in rats and rabbits. No evidence of neurotoxicity was seen in the studies available in the toxicity database.

Since the studies selected to establish the PODs did not identify a NOAEL (see Section 4.5), the 9,10-anthraquinone risk assessment team recommends that the 10X FQPA SF in the form of a UF_L be retained for all endpoints to account for LOAEL to NOAEL extrapolation.

4.4.1 Completeness of the Toxicology Database

The toxicology database for 9,10-anthraquinone is considered complete for evaluating and characterizing toxicity, assessing children's susceptibility under FQPA, and selecting endpoints for the current exposure pathways of concern. The database contains acceptable prenatal development studies in the rat and rabbit. Based on a WOE approach, considering all the available hazard and exposure data for 9,10-anthraquinone, the HASPOC recommended that the subchronic inhalation study in rats, subchronic study in dogs, acute and subchronic neurotoxicity studies, the two-generation reproduction study, and a comparative thyroid assay for 9,10-anthraquinone be waived (K. Yozzo, TXR 0057823, 1/29/2019; M. Zampariello, TXR 0058067, 1/12/2021; H. DeLeon, TXR 0058198, 7/29/2021).

4.4.2 Evidence of Neurotoxicity

There was no evidence of neurotoxicity in the available toxicity database for 9,10-anthraquinone, which included a subchronic toxicity study in rats that evaluated neurological parameters and neurohistopathology. Based on a WOE approach, HASPOC recommended that the neurotoxicity

[2] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

studies (both acute and subchronic) be waived for 9,10-Anthraquinone (M. Zampariello, TXR 0058067, 1/12/2021).

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

There is no evidence of increased susceptibility following *in utero* exposure to 9,10-anthraquinone in either the rat or rabbit developmental toxicity studies. All fetal effects were observed in the presence of maternal toxicity. In addition, the HASPOC recommended that the two-generation reproduction study be waived (M. Zampariello, TXR 0058067, 1/12/2021). The HASPOC also recommended that the comparative thyroid assay be waived (H. DeLeon, TXR 0058198, 7/29/2021).

4.4.4 Residual Uncertainty in the Exposure Database

Although there is some uncertainty in the dietary risk assessments due to incomplete residue chemistry and fate databases, as discussed in Section 2.1, the chronic non-cancer and cancer dietary assessments are not likely to underestimate dietary risks and an additional database uncertainty factor is not needed for this risk assessment. This is primarily due to (1) the number and magnitude of the conservative inputs that were incorporated into this risk assessment, (2) the fact that the rice use is only seed treatment and, therefore, residues in rice are expected to be relatively low, and (3) the supporting qualitative evidence provided by the sweet corn radiotracer study that the anticipated residue estimate used in the chronic non-cancer and cancer dietary assessments for rice grain (0.05 ppm) is not likely to greatly underestimate the potential total residue exposure for rice grain. The following factors, in the order of importance, further support this position: (1) EFED has acknowledged that clarification on the turf use and the additional fate data that are being required may also result in lower EDWCs than those used in this risk assessment (C. Sutton, D462175, 3/07/2022) and (2) future refinements to the percent crop treated assumption for rice used in this assessment (i.e., 100%) and the submission of rice processing data are expected to reduce exposure estimates used in this risk assessment or the potential for exposure for residues of concern in rice and secondary residues in livestock commodities. The residential exposure assessment is based on the Residential Standard Operating Procedures (SOPs) and incorporates chemical specific TTR data. These assessments are not likely to underestimate risks from exposures to 9,10-anthraquinone.

4.5 Toxicity Endpoint and Point of Departure Selections

Toxicity endpoints and PODs for dietary, residential, and occupational exposure scenarios are summarized below and in Table 4.5.3.1 - Table 4.5.3.2. All endpoints have been revised to reflect current policy and practice.

Acute Dietary Endpoint for All Populations: No endpoint attributable to a single dose was identified in the database; therefore, an acute dietary endpoint was not selected. The abortions observed in the rabbit developmental study occurred late (gestation days 25 and 28) and are not considered to be an acute effect. The acute neurotoxicity study was recommended to be waived.

Chronic Dietary Endpoint for All Populations: The chronic dietary endpoint for all populations was selected from the NTP carcinogenicity study in rats (MRID 48370301) with a LOAEL of 25 mg/kg/day (lowest dose tested) as the POD. A NOAEL was not established in the study. The POD is 25 mg/kg/day, based on decreased body weight in females, kidney histopathological effects, including hyaline droplet accumulation, nephropathy, pigmentation, renal tubular hyperplasia in females, and mineralization of medulla in females and males , as well as several liver histopathological effects, including cystic degeneration, inflammation, and eosinophilic and mixed-cell foci in both sexes, and cytoplasmic vacuolization in males. This study is appropriate for the population of concern and the duration of exposure. It is also protective of the chronic effects observed in the mouse study. The cPAD (equivalent to the chronic reference dose (RfD)) of 0.03 mg/kg/day was derived from a LOAEL of 25 mg/kg/day and a 1000-fold UF that included a 10X UF for inter-species extrapolations, a 10X UF for intra-species variations, and a 10X FQPA SF/UF_L applied for a LOAEL to NOAEL extrapolation.

Incidental Oral (Children 1 to <2 years of age) Short-Term (1-30 days) and Adult Oral Short-term (1-30 days) and Intermediate Term (1-6 months) Endpoints: The incidental oral and adult oral endpoints are based on the results from a subchronic toxicity study in rats (MRID 48708301). The POD is a LOAEL of 44 mg/kg/day based on decreased body weight in females. A NOAEL was not established in the study. The selected study is protective of all effects observed in the database following subchronic oral exposures. The residential LOC for MOE is 1000 based on a 10X UF for inter-species extrapolations, a 10X UF for intra-species variations, and a 10X FQPA SF/UF_L applied for a LOAEL to NOAEL extrapolation.

Short- (1-30 days) and Intermediate- (1-6 months) Term Dermal Endpoint for All Populations: A dermal endpoint was not selected. The effects observed in the 28-day dermal toxicity study in rats only occurred at the limit dose (1000 mg/kg/day), which is a dose that is not considered relevant for human health risk assessment. Target organs were evaluated in the dermal study. In addition, no increased susceptibility was seen in the developmental toxicity studies in rats or rabbits.

Short- (1-30 days) and Intermediate- (1-6 months) Term Inhalation: An inhalation toxicity study was recommended to be waived by HASPOC (K. Yozzo, TXR 0057823, 1/29/2019). The inhalation endpoint was based on the results from a subchronic oral toxicity study in rats (MRID 48708301). The POD is a LOAEL of 44 mg/kg/day based on decreased body weight in females. A NOAEL was not established in the study. The selected study is protective of all effects observed in the database following subchronic oral exposures. Since no inhalation absorption data are available, toxicity by the inhalation route is considered to be equivalent to the estimated toxicity by the oral route of exposure. The occupational/residential LOC for MOE is 1000 based on a 10X UF for inter-species extrapolations, a 10X UF for intra-species variations, and a 10X FQPA SF/UF_L applied for a LOAEL to NOAEL extrapolation.

4.5.1 Recommendation for Combining Routes of Exposures for Risk Assessment

When there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal, and inhalation exposures. The short-/intermediate-term oral and inhalation routes of exposures can be combined because the PODs

are based on the same endpoint of decreased body weight from a subchronic oral study in rats. A dermal endpoint was not selected.

4.5.2 Cancer Classification and Risk Assessment Recommendation

With regard to the *in vitro* mutagenic potential of 9,10-anthraquinone, the data on genotoxicity derived from different bacterial systems are conflicting. Results of the NTP and registrant sponsored bacterial mutagenicity tests (Ames tests) with 9,10-anthraquinone were mixed, with some samples giving negative results and others giving positive results. The contradictory results of anthraquinone may be attributable to variable amounts of contaminants or metabolites resulting from the different production methods of 9,10-anthraquinone (distillation/oxidation, Friedel-Crafts reaction, and Diels-Alder synthesis), purity of the test material, and/or testing methods (preincubation protocol or standard plate incorporation assay). The 9,10-anthraquinone test material for the NTP rodent bioassays was made by distillation of coal tar to obtain anthracene, followed by oxidation of the anthracene to form 9,10-anthraquinone. The test material manufactured by this method contains low levels of the mutagenic contaminant, 9-nitroanthracene. The registrant had proposed that the positive carcinogenic response in the NTP study was due to low levels of the mutagenic impurities associated with the manufacture of AQ from coal tar-derived anthracene and that mutagenicity is not associated with the current process (the Friedel-Crafts reaction) to manufacture 9,10-anthraquinone (MRID 50345101). A 97% pure grade of 9,10-anthraquinone obtained using the distillation/oxidation procedure was positive in the Ames test, and the further purified (99.8%) material tested in the NTP rodent bioassays showed mixed results. 9,10-anthraquinone purified to 100% was not mutagenic in the Ames tests. Additional Ames studies investigated the mutagenicity of the urinary metabolites of anthraquinone (1-hydroxyanthraquinone (which induces multi-target tumors in rats) and 2-hydroxyanthraquinone), possible contaminants, including 9-nitroanthracene, and samples of 9,10-anthraquinone produced by the other two manufacturing processes. Of the two metabolites, only 2-hydroxyanthraquinone was positive in the NTP Ames test, inducing the most powerful response in *Salmonella* strain TA98 (without metabolic activation). Other Ames test results showed mixed responses for the metabolites. These hydroxylated metabolites are formed within the body and are, therefore, unrelated to the manufacturing process or presence of impurities (R. Kent, TXR 0057759, D444252, 7/19/2018). 9-nitroanthracene produced a response in the Ames test. 9,10-anthraquinone prepared by the Diels-Alder process had conflicting result in the Ames Test, whereas 9,10-anthraquinone by the currently used Friedel-Crafts processes were negative in the Ames test. Despite the observed activity of 9,10-anthraquinone in some of these bacterial studies *in vitro*, the results were negative for *in vitro* gene mutations in mammalian cells (mouse lymphoma assay) in the absence of S9, *in vitro* chromosomal damage in mammalian Chinese Hamster Ovary cells, and *in vivo* mouse whole animal micronucleus bone marrow assays. There was a positive response in the mouse micronucleus peripheral blood *in vivo* assay. While no mode of action data were submitted, the carcinogenicity of the parent compound is not likely to be associated with a mutagenic MOA because it was negative in the whole animal bone marrow assays (J. Rowland and K. Middleton, TXR 0056478, 10/31/2012; R. Kent, TXR 0057759, D444252, 7/19/2018).

In accordance with the EPA's Final Guidelines for Carcinogenic Risk Assessment (March 2005), the CARC classified 9,10-anthraquinone as "Likely to be Carcinogenic to Humans." This

classification is based on the presence of kidney tumors in female rats, liver tumors in male and female mice, and thyroid tumors in male and female mice. Mutagenicity data shows that the major metabolite, 2-hydroxyanthraquinone, is mutagenic and may be responsible for the carcinogenic activity induced by 9,10-anthraquinone (J. Rowland and K. Middleton, TXR 0056478, 10/31/2012). A linear, low-dose approach extrapolation model (Q_1^*) was recommended for quantification of cancer risk to humans. The Q_1^* $(mg/kg/day)^{-1}$, of 9,10-anthraquinone based upon male mouse liver combined adenoma, carcinoma and hepatoblastoma tumor rates is 6×10^{-2} in human equivalents (L. Brunsman, TXR 0056576, D386881, 2/07/2013).

4.5.3 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.3.1. Summary of Toxicological Doses and Endpoints for 9,10-Anthraquinone for Use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	POD	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations)	No single dose effect was identified in the 9,10-anthraquinone database, therefore, an acute dietary endpoint was not selected.			
Chronic Dietary (All Populations)	LOAEL = 25 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF/ UF_L = 10X	Chronic RfD = 0.03 mg/kg/day cPAD = 0.03 mg/kg/day	NTP Carcinogenicity Study in F344 Rats (MRID 48370301) LOAEL = 20/25 mg/kg/day, M/F, based on decreased body weight in females. kidney histopathological effects, including hyaline droplet accumulation, nephropathy, pigmentation, renal tubular hyperplasia, and mineralization of medulla in females and mineralization of medulla in males, as well as several liver histopathological effects, including cystic degeneration, inflammation, and eosinophilic and mixed-cell foci in both sexes, and cytoplasmic vacuolization in males. NOAEL was not established.
Incidental Oral Short-Term (1-30 days) & Adult, Oral Short-term (1-30 days) and Intermediate-Term (1-6 months)	LOAEL = 44 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF/ UF_L = 10X	Residential LOC for MOE = 1000	Subchronic Oral Toxicity Study – Rat (MRID 48708301) LOAEL = 44 mg/kg/day based on decreased body weight in females. NOAEL was not established.

Table 4.5.3.1. Summary of Toxicological Doses and Endpoints for 9,10-Anthraquinone for Use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	POD	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short-Term (1-30 days) and Intermediate-Term (1-6 months)	A dermal endpoint was not selected. The effects observed in a 28-day dermal toxicity study in rats only occurred at a dose that is not relevant for human health risk assessment (1000 mg/kg/day) and no increased susceptibility was seen in the developmental toxicity studies in rats or rabbits. Dermal absorption factor (DAF) = 4%			
Inhalation Short-Term (1-30 days) and Intermediate-Term (1-6 months)	LOAEL = 44 mg/kg/day*	UF_A = 10X UF_H = 10X FQPA SF = 10X in the form of UF_L	Residential LOC for MOE = 1000	Subchronic Oral Toxicity Study – Rat (MRID 48708301) LOAEL = 44 mg/kg/day based on decreased body weight in females. NOAEL was not established.
Cancer (oral, dermal, inhalation)	Classification: "Likely to be Carcinogenic to Humans" based on kidney tumors in female rats, liver tumors in male and female mice, and thyroid tumors in male and female mice (J. Rowland and K. Middleton, TXR 0056478, 10/31/2012). The unit risk, Q_1^* $(mg/kg/day)^{-1}$, of anthraquinone based upon male mouse liver combined adenoma, carcinoma and hepatoblastoma tumor rates is 6×10^{-2} in human equivalents (L. Brunsman, TXR 0056576, D386881, 2/07/2013).			

Point of departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern.
* Inhalation toxicity is assumed equivalent to oral toxicity.

Table 4.5.3.2. Summary of Toxicological Doses and Endpoints for 9,10-Anthraquinone for Use in Occupational Human Health Risk Assessments.

Exposure/ Scenario	POD	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short-Term (1-30 days) and Intermediate-Term (1-6 months)	A dermal endpoint was not selected. The effects noted in a 28-day dermal toxicity study in rats occurred at a dose that is not relevant for human health risk assessment (1000 mg/kg/day)and no increased susceptibility was seen in the developmental toxicity studies in rats or rabbits. Dermal absorption factor (DAF) = 4%			
Inhalation Short-Term (1-30 days) and Intermediate-Term (1-6 months)	LOAEL = 44 mg/kg/day*	UF_A = 10X UF_H = 10X UF_L = 10X	Occupational LOC for MOE = 1000	Subchronic Oral Toxicity Study – Rat (MRID 48708301) LOAEL = 44 mg/kg/day based on decreased body weight in females. NOAEL was not established.

Table 4.5.3.2. Summary of Toxicological Doses and Endpoints for 9,10-Anthraquinone for Use in Occupational Human Health Risk Assessments.				
Exposure/ Scenario	**POD**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Cancer (oral, dermal, inhalation)	Classification: "Likely to be Carcinogenic to Humans" based on kidney tumors in female rats, liver tumors in male and female mice, and thyroid tumors in male and female mice (J. Rowland and K. Middleton, TXR 0056478, 10/31/2012). The unit risk, Q_1^* $(mg/kg/day)^{-1}$, of anthraquinone based upon male mouse liver combined adenoma, carcinoma and hepatoblastoma tumor rates is 6×10^{-2} in human equivalents (L. Brunsman, TXR 0056576, D386881, 2/07/2013).			

Point of departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. MOE = margin of exposure. LOC = level of concern.
* Inhalation toxicity is assumed equivalent to oral toxicity.

Body Weight

The standard body weight for the general population (80 kg) was used for all exposure scenarios covered in this risk assessment since the endpoints selected were not female-specific, developmental, and/or fetal effects. The child-specific (1 to <2 years old) body weight (11 kg) was also used.

4.6 Endocrine Disruptor Screening Program

As required by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (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 reregistration decision for 9,10-anthraquinone, 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), anthraquinone 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 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[3] 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.

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.[4]

5.0 Dietary Exposure and Risk Assessment

5.1 Residues of Concern Summary and Rationale

The seed treatment use of 9,10-anthraquinone on rice is the only food/feed use of 9,10-anthraquinone (B. Cropp-Kohlligian, D461484, 6/03/2021; ChemSAC meeting 5/26/2021). The residue chemistry and environmental fate databases for 9,10-anthraquinone are incomplete. The nature of the residue in plants (primary and rotational crops) and livestock for 9,10-anthraquinone has not been delineated. Multiple environmental fate studies required for outdoor terrestrial uses such as the turf use have not been submitted, including anaerobic aquatic metabolism data and sorption data which are needed for modeling. A Residues of Concern Knowledgebase Subcommittee (ROCKS) meeting was not held for 9,10-anthraquinone. At this time, HED and EFED have determined that, based on the available limited data, only residues of the parent compound, 9,10-anthraquinone, are included in this risk assessment as residues of concern in rice commodities and drinking water. HED and EFED are requiring additional data to confirm this determination; however, once the residue chemistry and environmental fate databases for 9,10-anthraquinone are complete, additional metabolites and/or degradates may be residues of concern in future risk assessments for 9,10-anthraquinone.

Based on the available ADME data (see Section 4.2), the only significant metabolites identified in the rat were 1-hydroxyanthraquinone and 2-hydroxyanthraquinone. Both of the hydroxy metabolites have similar structures as the parent compound, so are assumed to have equal toxicity. In addition, 2-hydroxyanthraquinone is a bacterial mutagen and 1-hydroxyanthraquinone is reported to induce tumors in rats (see Section 4.5.2). Based on the review of the available limited residue chemistry (see Section 5.2 for a summary of the available residue chemistry data) and environmental fate data, dietary exposure to these metabolites (i.e., free forms) from rice commodities and drinking water resulting from the registered uses of 9,10-anthraquinone assessed as part of registration review is expected to be negligible compared to the parent. The required residue chemistry and fate data are needed to confirm this finding.

[3] See https://www regulations.gov/document?D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.

[4] https://www.epa.gov/endocrine-disruption

EFED summarized the available fate data in the following memorandum: "Anthraquinone: Drinking Water Exposure Assessment in Support of Registration Review" (C. Sutton, D462175, 3/07/2022). In brief, "while 1-hydroxyanthraquinone and 2-hydroxyanthraquinone may form from 9,10-anthraquinone, only the former compound was detected in the available environmental fate data. In the aqueous photolysis study, 1-hydroxyanthraquinone was a maximum of 19.4% at 1-hour post-treatment but was below the limit of detection (LOD) by 8 hours so was not an exposure concern. In the aerobic aquatic study, 1-hydroxyanthraquinone appeared only sporadically in the two study systems. It was detected in three replicates at <1% in one system and at a maximum of 3.1-3.9% at a single interval plus <1% in three additional replicates throughout the 209-day study in the second system. Based on negligible exposure, 1-hydroxyanthraquinone was not included as a residue of concern for drinking water."

There are no livestock metabolism or feeding study data available to determine if finite residues of 9,10-anthraquinone are expected in livestock commodities; hence, residues of 9,10-anthraquinone in livestock commodities were not included in this assessment. Assuming that the required plant metabolism data confirms that only parent is a residue of concern in rice, livestock maximum reasonably balanced diets, even assuming 100% crop treated, are not very high. Additional data are being required to confirm this determination; however, once the residue chemistry database for 9,10-anthraquinone is complete, 9,10-anthraquinone residues of concern in livestock commodities may be included in future risk assessments for 9,10-anthraquinone.

5.2 Food Residue Profile

The residue chemistry database for 9,10-anthraquinone is incomplete. The available guideline data are limited to a sweet corn radiotracer study to support the sweet corn and field corn seed treatment uses (MRID 51302904; B. Cropp-Kohlligian, D459655, 3/17/2021) and a rice field trial study to support the rice seed treatment use (MRID 48317201; B. Cropp-Kohlligian, D461484, 6/03/2021). The United States Department of Agriculture (USDA) also provided some reports of non-guideline, non-GLP unpublished/published efficacy studies which also included some very limited field trial information (J. Kidwell, *et al.,* D457252, 7/27/2021). At this time, no tolerances for residues of 9,10-anthraquinone have been established.

The nature of the residue in plant for 9,10-anthraquinone has not been delineated. However, based on the available data taken together, residues of the parent, 9,10-anthraquinone, may be readily taken up by plants grown from 9,10-anthraquinone treated seed. As a general rule for seed treatment uses, if residues of concern are taken up into raw agricultural commodities (RACs) of a crop at levels <0.005 ppm then that use is considered a nonfood/nonfeed use and if residues are ≥0.005 ppm (i.e., the trigger value for food/feed use determination is 0.005 ppm) then that use is considered a food/feed use (Seed-Treatment Focus Group (STFG) Guidance Document, G. Kramer *et al*., 1/26/2018).

The available sweet corn radiotracer study conducted at the maximum seed treatment use rate on corn (i.e., 0.005 lb ai/lb seed (rounded)), found that total radioactive residues (TRR) were <0.005 ppm in/on all regulated corn RACs, including the grain (i.e., 0.003 ppm). Hence, the currently registered seed treatment uses of 9,10-anthraquinone on field and sweet corn are considered nonfood/nonfeed uses in accordance with current guidance.

The HED Chemistry Scientific Advisory Council (ChemSAC meeting 5/26/2021) determined that, based on the available rice field trial study, the use on rice assessed as part of registration review (AV-5055; EPA Reg. No. 69969-7; 0.003 lb ai/lb seed (rounded)) is a food/feed use. At this time, no tolerances for residues of 9,10-anthraquinone may be established due the lack of adequate data to support the establishment of any tolerances. Based on the available rice field trial study, residues of 9,10-anthraquinone, free 1-hydroxyanthraquinone, and free 2-hydroxyanthraquinone in/on rice grain from the use of 9,10-anthraquinone (i.e., 0.003 lb ai/lb seed (rounded)) on rice are expected to be less than the limit of quantitation (LOQ) of the data-collection method for 9,10-anthraquinone (i.e., <0.05 ppm) but detectable (i.e., above the LOD; >0.022 ppm) and the <LODs of the data-collection method for free 1-hydroxyanthraquinone (<0.018 ppm) and free 2-hydroxyanthraquinone (<0.014 ppm). [Note: The study did not look for conjugates of 1-hydroxyanthraquinone or 2-hydroxyanthraquinone; hence, it is unknown if these are rice metabolites.] The rice field trials were conducted at an exaggerated rate (2.6x) relative to the use on rice assessed as part of registration review (i.e., 0.003 lb ai/lb seed (rounded)); however, data from the rice field trial study also indicate that proportionality (i.e., adjusting field trial results from trials conducted at rates different than 1X (good agricultural practices (GAP) or label) to 1X (ChemSAC Minutes, March 28, 2012) could not be applied to this study and is not appropriate for these 9,10-anthraquinone residue data. The appropriateness of applying proportionality for the free 1-hydroxyanthraquinone and free 2-hydroxyanthraquinone residue data could not be determined. For the purposes of the chronic non-cancer and cancer dietary risk assessments, anticipated residues of 9,10-anthraquinone in/on rice commodities were estimated from the rice field trial data at 0.05 ppm. Residues of free 1-hydroxyanthraquinone and free 2-hydroxyanthraquinone in/on rice commodities were not included in the dietary risk assessment, since they were found at levels below the LODs of the data-collection method used in the rice study.

No plant or rice metabolism data have been submitted for 9,10-anthraquinone and the nature of the residue in plants is not known; however, residues resulting from seed-treatment uses are expected to be relatively low. The only chemical-specific radiolabel study available is the sweet corn radiotracer study. In general, it is not appropriate to translate corn seed treatment data to other cereal grains (STFG Guidance Document, G. Kramer *et al*., 1/26/2018) since there is the potential for corn data to underestimate residues in small grain cereals and rice. Although strictly not appropriate for quantitative purposes, based on seeding rates per acre and minimum crop yield per acre provided in Appendix 3 of the STFG Guidance Document (G. Kramer *et al*., 1/26/2018), residues in rice grain may be at least 6x or more than residues in sweet corn when seed treatment use rates on rice and sweet corn are similar. Hence, qualitatively, given the findings of the chemical-specific sweet corn radiotracer study conducted at 0.005 lb ai/lb seed which found TRR of 0.003 ppm in/on corn grain, total residues of concern in/on rice grain from seed treatment use at 0.003 lb ai/lb seed (rounded) may be expected to be well above the food/feed trigger value (i.e., >0.005 ppm) but are still likely to be relatively low. Hence, the sweet corn radiotracer study is qualitative evidence that the anticipated residue estimate used in the dietary assessments for rice grain (0.05 ppm) is not likely to greatly underestimate the potential total residue exposure in/on rice grain. [Note: While the sweet corn radiotracer study may be used to provide qualitative characterization for the chronic non-cancer and cancer dietary assessments regarding how low total residues in/on rice grain may be, they do not supersede the chemical/crop-specific rice field trial data for quantitating residues of parent in/on rice grain.]

No processing data for 9,10-anthraquinone have been submitted; however, maximum theoretical concentration factors for the processed commodities of rice grain listed in Table 1 of OCSPP Guideline 860.1000 (i.e., polished rice (rice, white) and bran) have been used to estimate residues of parent, 9,10-anthraquinone, in these processed commodities of rice for this assessment. Maximum theoretical concentration factors for polished rice (white rice) and rice bran are 1.5x and 7.7x, respectively (B. Cropp-Kohlligian, D462831, 3/08/3022).

No livestock metabolism or feeding study data have been submitted for 9,10-anthraquinone. Rice grain and rice bran are carbohydrate concentrates (CC) that may be fed to all livestock. [Note: Rice hulls and straw are no longer considered significant feedstuffs.] Assuming that the required plant metabolism data confirms that only parent is a residue of concern in rice, livestock maximum reasonably balanced diets (RBDs), even assuming 100% crop treated and, due to the absence of rice processing data, a maximum theoretical concentration factor for rice bran (7.7x), are not very high and are estimated at 0.08 ppm for cattle (beef and dairy) and 0.05 ppm for swine and poultry. These RBDs estimates are driven by the unrefined contribution estimate from rice bran. There are no livestock metabolism or feeding study data available to determine if finite residues of 9,10-anthraquinone are transferred to livestock commodities from consumption of rice feed stuffs treated with 9,10-anthraquinone to the extent that tolerances are needed for livestock commodities. Hence, in the absence of any evidence that residues of 9,10-anthraquinone transfer to livestock, residues of 9,10-anthraquinone in livestock commodities were not included in the dietary assessment. Additional data are being required to confirm this determination. Additionally, it should be noted that should livestock commodities need to be included in future chronic non-cancer and cancer dietary risk assessments, those anticipated residue estimates would be further refined/reduced to include PCT and are expected to be very low for that reason.

No rotational crop data have not been submitted for 9,10-anthraqunone. Taken together, the available data indicate that residues of 9,10-anthraquinone may be readily taken up by plants from 9,10-anthraquinone treated seed (B. Cropp-Kohlligian, D461484, 6/03/2021). Hence, the potential for residues of 9,10-anthraquinone to be taken up by rotated crops cannot be dismissed. Pending submission of the required confined accumulation in rotational crop data (OCSPP Guideline 860.1850), all 9,10-anthraquinone labels registered for use on crops should be revised to restrict rotation to only those crops for which 9,10-anthraquinone is already registered for use (corn (field and sweet) and rice). A 365-day plantback interval (PBI) should be imposed for all other crops. These label restrictions should ensure that there is no exposure to residues of 9,10-anthraquinone from rotational crop sources.

5.3 Water Residue Profile

The EDWCs for 9,10-anthraquinone (parent only) used in this dietary risk assessment were provided by the EFED in the following memorandum: “Anthraquinone: Drinking Water Exposure Assessment in Support of Registration Review” (C. Sutton, D462175, 3/07/2022) and incorporated directly into this dietary assessment. Water residues were incorporated in the DEEM-FCID into the food categories “water, direct, all sources” and “water, indirect, all sources.”

The maximum EDWCs for acute, chronic, and cancer risk are associated with surface water sources of drinking water. For surface water sources of drinking water, the **acute 1-in-10-year daily average and the chronic 1-in-10-year annual average EDWCs are 27.52 µg/L and 1.61 µg/L**, respectively. The **cancer 30-year average EDWC is 1.26 µg/L**. The EDWCs in surface water sources of drinking water were generated using the Pesticide in Water Calculator (PWC v2.001; May 2021), a graphical user interface shell integrating the Pesticide Root Zone Model (PRZM v.5.02) and the Variable Volume Water Model (VVWM v.1.02.1). The model was used with the standard turf scenarios already available from PWC model v.1.52, as new turf scenarios have not yet been developed. A percent crop area (PCA) of 100% was used.

Table 5.3.1. Highest EDWCs for 9,10-Anthraquinone (parent only).

Model and Scenario (Application Details)	Use	Application Rate lbs a.i./A x No. of Apps	EDWCs[1,2,3] in µg/L		
			Acute	Chronic	Cancer
Surface Water					
PWC, PAturfStd - (High boom, Typical Timing)	Turf	1.03 x 7	**27.52**	**1.61**	**1.26**
Groundwater					
PWC, FL Central Ridge	Turf	1.03 x 7	0.033	None	

PWC-Pesticide in Water Calculator

[1] Bolded values are the recommended EDWCs for use in the HED dietary assessment. The only residue of concern is 9,10-anthraquinone.

[2] For surface water modeling, the acute concentration is provided as the 1-in-10-year daily mean, the chronic concentration is the 1-in-10-year annual mean, and the cancer number is the 30-year mean concentration. For groundwater simulations, the acute number is the highest daily value and the chronic and cancer EDWC is the post-breakthrough average concentration. None = no value determined since throughputs were less than one even with a 100-year simulation and the high K_{OC} of 5012 L/kg-organic carbon indicates groundwater exposure is not a major concern.

[3] This assessment is based on the use of 9,10-anthraquinone on turf using the end-use product AV-5055 (EPA Registration No. 69969-7).

The drinking water models and their descriptions are available at the EPA internet site: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/about-water-exposure-models-used-pesticide.

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

Chronic non-cancer and cancer dietary (food (rice only) and drinking water) exposure and risk assessments for residues of 9,10-anthraquinone were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 4.02. This software uses 2005-3-2010 food consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America (NHANES/WWEIA). The DEEM-FCID analyses estimate the dietary exposure and risk of the general U.S. population and various population subgroups. The results reported in

Table 5.4.6.1 are for the general U.S. Population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, females 13-49, adults 20-49, and adults 50-99 years.

Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. For acute and chronic assessments, the risk is expressed as a percentage of a maximum acceptable dose (i.e., the dose that HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population-adjusted dose (PAD). The PAD is equivalent to the POD divided by all applicable UFs, including the FQPA SF. For acute and non-cancer chronic exposures, HED is concerned when estimated dietary risk exceeds 100% of the PAD.
It should be noted that, given that the residue chemistry and environmental fate databases for 9,10-anthraquinone are incomplete, there is uncertainty as to: (1) whether additional metabolites and/or degradates of 9,10-anthraquinone in rice commodities and/or drinking water are of concern for chronic non-cancer and/or cancer dietary risk and (2) whether finite residues of concern for chronic non-cancer and/or cancer dietary risk may be incurred in livestock (cattle (beef and dairy), swine, and poultry) commodities due to consumption by livestock of rice feed stuffs treated with 9,10-anthraquinone. HED notes that based on the available limited residue chemistry and environmental data, dietary exposure to residues of free 1-hydroxyanthraquinone or free 2-hydroxy-anthraquinone, the only significant metabolites identified in the ADME data (see Section 4.2), from rice commodities and drinking water resulting from the registered uses of 9,10-anthraquinone assessed as part of registration review is expected to be negligible compared to the parent. While there is the potential for other metabolites and/or degradates of 9,10-anthraquinone in rice and drinking water, it is uncertain as to whether any would be considered significant for chronic non-cancer dietary exposure or to have carcinogenic potential. Additional residue chemistry and fate data are being required to confirm that only residues of parent are of concern in rice and drinking water. In the absence of livestock metabolism or feeding study data available to determine if finite residues of 9,10-anthraquinone are expected in livestock commodities; residues of 9,10-anthraquinone in livestock commodities were not included in this assessment. Assuming that the required plant metabolism data confirms that only parent is a residue of concern in rice, livestock maximum reasonably balanced diets, even assuming 100% crop treated, are not very high. Additional data are being required to confirm this determination for livestock commodities. Although there is some uncertainty in the dietary risk assessments due to incomplete residue chemistry and fate databases, the chronic non-cancer and cancer dietary assessments are not likely to underestimate dietary risks given the number of conservative assumptions that were incorporated into the assessments.

5.4.2 Percent Crop Treated Used in Dietary Assessment

In the absence of any percent crop treated data, HED assumed that all commodities would be treated to a level of 100% for the chronic non-cancer and cancer dietary exposure assessments.

5.4.3 Acute Dietary Risk Assessment

An acute dietary endpoint was not selected; therefore, an acute dietary exposure assessment was not required.

5.4.4 Chronic Dietary Risk Assessment

The chronic non-cancer dietary exposure assessment for residues of 9,10-anthraquinone (parent only) in rice commodities and drinking water is unrefined. Residues of 9,10-anthraquinone in/on rice commodities were estimated from field trial data and based on the maximum residue found in/on rice grain (0.05 ppm) (MRID 49620401; B. Cropp-Kohlligian, D461484, 6/03/2021). Default processing factors were used for rice, brown (1.25x) and rice, flour (1.25x) and, in the absence of processing data, maximum theoretical concentration factors were used for rice, bran (7.7x) and rice, white (1.5x). In the absence of any percent crop treated data, the analysis assumed 100% crop treated. EFED provided a conservative EDWC of 1.61 ppb for 9,10-anthraquinone for the chronic non-cancer dietary assessment. The general U.S. population and all population subgroups use <1% of the cPAD. The results of the chronic non-cancer dietary (food (rice only) and drinking water) exposure and risk assessment are reported in Table 5.4.6.1 below. The results of the chronic non-cancer dietary (rice only) exposure and risk assessment are reported in Table 5.4.6.2 below.

5.4.5 Cancer Dietary Risk Assessment

The cancer dietary exposure assessment for residues of 9,10-anthraquinone (parent only) in rice commodities and drinking water is unrefined. It used the same inputs for residues of 9,10-anthraquinone in/on rice commodities as the chronic non-cancer dietary exposure assessment. EFED provided a conservative EDWC of 1.26 ppb for 9,10-anthraquinone for the cancer dietary assessment. HED reports cancer risk for the adult population subgroup with the highest cancer risk estimate. For 9,10-anthraquinone, that subgroup is adults 20-49, which has a cancer risk estimate of 3×10^{-6}; white rice and drinking water contributed 41% and 54%, respectively, to the total exposure estimate. The cancer risk estimate for residues of 9,10-anthraquinone (parent only) in rice commodities only is 1×10^{-6}. The results of the cancer dietary (food (rice only) and drinking water) exposure and risk assessment are reported in Table 5.4.6.1 below. The results of the cancer dietary (rice only) exposure and risk assessment are reported in Table 5.4.6.2 below.

5.4.6 Summary Table

5.4.7

Table 5.4.6.1. Summary of Dietary (Food (Rice[1] Only) and Drinking Water) Exposure and Risk for 9,10-Anthraquinone (parent only).

Population Subgroup	Acute Dietary		Chronic Non-Cancer Dietary		Cancer[2]	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	No acute endpoint		0.000052	<1	N/A	N/A
All Infants (<1 year old)			0.000175			
Children 1-2 years old			0.000086			
Children 3-5 years old			0.000071			
Children 6-12 years old			0.000048			
Youth 13-19 years old			0.000036			
Adults 20-49 years old			0.000053		**0.000047**	**3 x 10^{-6}**
Adults 50+ years old			0.000043		0.000037	
Females 13-49 years old			0.000047		0.000040	

Table 5.4.6.1. Summary of Dietary (Food (Rice[1] Only) and Drinking Water) Exposure and Risk for 9,10-Anthraquinone (parent only).						
Population Subgroup	**Acute Dietary**		**Chronic Non-Cancer Dietary**		**Cancer[2]**	
	Dietary Exposure (mg/kg/day)	**% aPAD**	**Dietary Exposure (mg/kg/day)**	**% cPAD**	**Dietary Exposure (mg/kg/day)**	**Risk**

Table 5.4.6.2. Summary of Dietary (Food (Rice[1] Only)) Exposure and Risk for 9,10-Anthraquinone (parent only).						
Population Subgroup	**Acute Dietary**		**Chronic Non-Cancer Dietary**		**Cancer[2]**	
	Dietary Exposure (mg/kg/day)	**% aPAD**	**Dietary Exposure (mg/kg/day)**	**% cPAD**	**Dietary Exposure (mg/kg/day)**	**Risk**
General U.S. Population	No acute endpoint		0.000019	<1	N/A	N/A
All Infants (<1 year old)			0.000055			
Children 1-2 years old			0.000042			
Children 3-5 years old			0.000035			
Children 6-12 years old			0.000021			
Youth 13-19 years old			0.000013			
Adults 20-49 years old			0.000021		**0.000021**	**1×10^{-6}**
Adults 50+ years old			0.000012		0.000012	7×10^{-7}
Females 13-49 years old			0.000015		0.000015	9×10^{-7}

[1] AV-1011® Rice Seed Treatment (EPA Registration No. 69969-4; cancelled 9/7/2021) allowed seed treatment use of 9,10-anthraquinone on rice and was only recently cancelled. This cancelled end-use product allowed for a higher use rate on rice seed than the only currently registered end-use product for use on rice, AV-5055 (EPA Registration No. 69969-7).
Note: While this assessment is based on the use of 9,10-anthraquinone for the currently registered end-use product AV-5055 (EPA Registration No. 69969-7), the residue estimates for rice commodities used in both the chronic non-cancer and cancer dietary assessments are the same inputs and would also cover residues for rice commodities resulting from the higher use rate of the now cancelled end-use product, AV-1011® Rice Seed Treatment (EPA Registration No. 69969-4; cancelled 9/7/2021).
[2] Bolded is the most highly exposed adult population for the cancer dietary assessment.

6.0 Residential Exposure/Risk Characterization

Residential exposures are expected from the registered uses of 9,10-anthraquinone. Residential post-application exposure assessments were conducted based on the registered turf uses including home lawns, golf courses, and parks.

6.1 Residential Handler Exposure/Risk Estimates

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are addressed somewhat differently by HED as homeowners are assumed to complete all elements of an application without use of any protective equipment.

The registered 9,10-anthraquinone product label (EPA Reg. No. 69969-7) with residential use sites (e.g., lawn, parks, sports fields, and golf course turf) requires that handlers wear specific clothing (e.g., long-sleeve shirt/long pants) and/or use PPE. Therefore, HED has made the assumption that these products are not for homeowner use, and has not conducted a quantitative residential handler assessment.

6.2 Residential Post-Application Exposure and Risk Estimates

There is the potential for post-application exposure for individuals exposed as a result of being in an environment that has been previously treated with 9,10-anthraquinone. The quantitative exposure/risk assessment for residential post-application exposures is based on the scenarios listed in Table 6.2.2.

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[5]. While not the only lifestage potentially exposed for these post-application scenarios, the lifestage that is included in the quantitative assessment is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

Residential Post-application Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. Each assumption and factor is detailed in the 2012 Residential SOPs[5].

Application Rate:
Maximum single application rates for residential scenarios can be found in Table 3.3.

Exposure Duration:
Residential post-application exposure is expected to be short-term in duration. Intermediate-term exposures are not likely.

Turf Transferable Residue (TTR) Data: A chemical-specific TTR study ("Determination of Turf Transferable Residues (TTR) on Turf Treated with FlightControl Plus," EPA MRID 48639805) was submitted for 9,10-anthraquinone. The TTR study was reviewed and found to be acceptable for risk assessment (A. Rivera-Lupiáñez, D396314, 10/12/2012). The data from this study were used to assess non-cancer and cancer post-application exposure from the registered turf uses of 9,10-anthraquinone. The predicted day-0 residue was adjusted in the post-application assessment for any differences between the study application rate and the registered application rate for 9,10-anthraquinone. A regression analysis was completed as part of this assessment and is detailed in Appendix C of the Occupational and Residential Exposure (ORE) document that supports this risk assessment (B. Van Deusen, D462829, 3/08/2022).

The data and the results of the pseudo first-order statistical analysis are summarized below in Table 6.2.1. The Georgia site had the most protective predicted initial concentration and percent of transferable active ingredient (0.567 µg/cm^2; 1.27% of application), and was used for the purpose of the turfgrass post-application risk assessments. The predicted DAT-0 (0 days after treatment) residue value was adjusted to account for the maximum registered turf application rate (Application Adjustment Factor = maximum application rate/study application rate, where the maximum registered application rate is 1.03 lbs ai/A).

[5] Available: http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Table 6.2.1. Review of Dissipation of Turf Transferrable Residues of 9,10-anthraquinone on Turf (MRID 48639805).			
Statistic	**Pennsylvania**	**Georgia**	**California**
Application Rate (lbs ai/A) Last (Fourth) Application	4.06	3.97	3.99
Measured Average Day 0 Residue (µg/cm^2)	0.493	0.708	0.572
Predicted Day 0 Residue (µg/cm^2)	0.492	**0.567**[1]	0.503
Slope	-0.057	-0.042	-0.033
Half-Life (days)	12.2	16.4	21.3
R^2	0.8889	0.8272	0.5678

1 **Bold** text indicates value considered for use in risk assessment.

Residential Post-application Non-Cancer Exposure and Risk Equations

The algorithms used to estimate residential post-application exposure and dose can be found in the 2012 Residential SOPs[6].

Combining Non-Cancer Exposure and Risk Estimates

Residential post-application non-cancer dermal (adults and children) and incidental oral (children) exposure is anticipated from registered 9,10-anthraquinone uses, however there was no dermal POD selected. Therefore, only children's (1 to <2 years old) incidental oral exposures have been quantitatively assessed and there are no additional routes to combine. The incidental oral scenarios (i.e., hand-to-mouth (HTM) and object-to-mouth (OTM)) should be considered inter-related and it is likely that they occur interspersed amongst each other across time.

Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates

All residential post-application non-cancer incidental oral exposures resulted in no risk estimates of concern (i.e., MOEs ≥ LOC; LOC = 1,000) for children (1 to <2 years old) with MOEs ranging from 2,200 to 1,300,000 using chemical-specific TTR data. Table 6.2.2 below presents the residential post-application exposure and risk estimates for 9,10-anthraquinone.

Table 6.2.2. Residential Post-application Non-cancer Exposure and Risk Estimates for 9,10-anthraquinone Using Chemical-Specific TTR Data.						
Lifestage	**Post-application Exposure Scenario**		**Application Rate**[1]	**Dose (mg/kg/day)**[2]	**MOEs**[3] **(LOC = 1,000)**	**Combined MOEs**
	Use Site	**Route of Exposure**				
Child	Turf[4]	HTM	1.03	0.0199	2,200	NA
		OTM		0.0006	72,000	
		Soil Ingestion		0.000035	1,300,000	

1 Based on registered label (Reg. No. 69969-7).
2 Dose (mg/kg/day) algorithms provided in 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 MOE = POD (44 mg/kg/day) ÷ Dose (mg/kg/day).
4 Using TTR data MRID 48639805, A. Rivera-Lupiáñez, D396314, 10/12/2012.

[6] http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

Residential Post-application Cancer Exposure and Risk Estimate Equations

Although a non-cancer dermal risk assessment was not performed because a dermal endpoint was not selected, a dermal cancer exposure and risk assessment was performed because dermal exposure contributes to the overall cancer risk for 9,10-anthraquinone.

Post-application cancer risk estimates for adults were calculated using a linear low-dose extrapolation approach in which a lifetime average daily dose (LADD) is first calculated and then multiplied by a Q_1* that has been calculated for 9,10-anthraquinone based on dose response data in the appropriate toxicology study (Q_1* = 6 x 10^{-2} $(mg/kg/day)^{-1}$). As residential post-application inhalation exposures are not expected, only a dermal LADD was calculated applying a DAF of 4%. The algorithms used to estimate the LADD and cancer risk for residential post-application exposure can be found in Appendix B of the ORE document that supports this risk assessment (B. Van Deusen, D462829, 3/08/2022).

For the residential post-application cancer assessments, 2 average residue values are presented. The residue values used to calculate the exposure were derived from a 365-day residue average assuming 7 applications in the year (registered maximum number of applications) and 4 applications in the year based on registrant submitted information (Email from P. Di Salvo to B. Van Deusen on 3/05/2021), both at a 14-day re-treatment interval based on label directions.

Days Per Year of Exposure:

Based on HED default values for frequency of exposure, adults are expected to be exposed to 9,10-anthraquinone from residential turf uses while performing the following activities:

- High contact lawn activities – 120 days per year
- Mowing activities – 17 days per year
- Golfing activities– 52 days per year

Years Per Lifetime of Exposure:

It is assumed that adults would be exposed for 50 years out of a 78-year lifespan.

High Contact Lawn Activities:

The residential turf post-application SOP provides a standard method for estimating exposure from dermal contact with turf that has been previously treated with pesticides. This scenario assumes that pesticide residues are transferred to the skin of adults who enter treated lawns for play, recreation, yardwork, or other homeowner activities. The transfer coefficients used for the dermal scenarios were derived from data gathered while adult human volunteers performed an approximate 2-hour composite routine consisting of 12 sequential activities which children and adults routinely engage on residential turf. These activities represent behaviors that are reported in the National Human Activity Pattern Survey (NHAPS). Based on data from the Exposures Factors Handbook 2011 Edition, the recommended point estimate for use in post-application dermal exposure assessment for adults and children is 1.5 hrs/day. The transfer coefficient and exposure time values are used to obtain a dermal dose which is then used with the other assumptions and inputs described above to determine a LADD and cancer risk estimate.

Summary of Residential Post-application Cancer Exposure and Risk Estimates

Table 6.2.3 provides a summary of the residential post-application cancer risk estimates for registered turf uses of 9,10-anthraquinone. Residential post-application cancer risk estimates using the maximum registered application rates and 7 applications per year, range from 2×10^{-4} to 5×10^{-7}.

Table 6.2.3. Residential Post-application Cancer Exposure and Risk Estimates for 9,10-anthraquinone.

Lifestage	Post-application Exposure Scenario		Dermal LADD (mg/kg/day)[1]	Cancer Risk Estimate (7 apps/year)[2]	Cancer Risk Estimate (4 apps/year)[3]
Adult	Turf – Liquid High Contact Lawn Activities	Dermal	0.0028	$2x10^{-4}$	$1x10^{-4}$
Adult	Turf – Liquid Mowing		0.0000081	$5x10^{-7}$	$3x10^{-7}$
Adult	Turf – Liquid Golfing		0.000096	$6x10^{-6}$	$3x10^{-6}$

1 Dermal LADD (mg/kg/day) = Dermal dose (mg/kg/day) × [Days per year of exposure (120, 17, or 52 days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (50 yrs) ÷ Lifetime expectancy (78 yrs)].
2 Cancer risk estimates = Total LADD × Q_1^*, where $Q_1^* = 6x10^{-2}$ $(mg/kg/day)^{-1}$. Using labeled maximum 7 applications per year.
3 Cancer risk estimates = Total LADD × Q_1^*, where $Q_1^* = 6x10^{-2}$ $(mg/kg/day)^{-1}$. Using average of 4 applications per year.

6.3 Residential Risk Estimates for Use in Aggregate Assessment

Table 6.3.1 reflects the non-cancer residential risk estimate that is recommended for use in the aggregate assessment for 9,10-anthraquinone.

- The recommended residential exposure for use in the children 1<2 years old non-cancer aggregate assessment is hand-to-mouth exposures from post-application exposure to turf.

Table 6.3.1. Recommendations for the Residential Exposures for the 9,10-anthraquinone Non-Cancer Aggregate Assessment.

Lifestage	Exposure Scenario	Dose (mg/kg/day)[1]				MOE[2]			
		Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total
Child	Post-application high contact activities on turf	NA	NA	0.0199	**0.0199**	NA	NA	2,000	**2,200**

1 Dose = the highest dose for each applicable lifestage of all residential scenarios assessed. Total = dermal + inhalation + incidental oral (where applicable).
2 MOE = the MOEs associated with the highest residential doses. Total = 1 ÷ (1/Dermal MOE) + (1/Inhalation MOE) + (1/Incidental Oral MOE), where applicable.

Table 6.3.2 reflects the cancer residential risk estimate that is recommended for use in the aggregate assessment for 9,10-anthraquinone.

- The recommended residential exposure for use in the adult cancer aggregate assessment is dermal exposures from post-application exposure to turf.

Table 6.3.2. Recommendations for the Residential Exposures for the 9,10-anthraquinone Cancer Aggregate Assessment.

Lifestage	Exposure Scenario	LADD (mg/kg/day)[1]				Residential Cancer Risk Estimate[2]
		Dermal	Inhalation	Oral	Total	
Adult	Post-application high contact activities on turf	0.0028	NA	NA	**0.0028**	**$2x10^{-4}$**

1 Dermal LADD (mg/kg/day) = Dermal dose (mg/kg/day) × [Days per year of exposure (days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (50 yrs) ÷ Lifetime expectancy (78 yrs)].
2 Cancer risk estimates = Total LADD × Q_1^*, where $Q_1^* = 6x10^{-2}$ $(mg/kg/day)^{-1}$.

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. Dietary (food + drinking water) and residential exposures from 9,10-anthraquinone have been aggregated since those exposure pathways are relevant for risk assessment.

7.1 Acute Aggregate Risk

An acute dietary endpoint (i.e., single dose endpoint) for risk assessment was not identified in the toxicity database for the general U.S. population or any other subpopulation; therefore, an acute aggregate assessment was not conducted.

7.2 Short-Term Aggregate Risk

Short-term aggregate assessments include exposures that will occur from one to thirty days. There is potential for residential exposure to 9,10-anthraquinone from registered turf uses including home lawns, golf courses, and parks. The potential short-term residential exposure scenarios (high contact activities on treated turf) and risk estimates that are recommended for aggregate assessment are discussed in detail above in Section 6.3. For the non-cancer aggregate assessment, the residential exposure involves hand-to-mouth exposure activities from post-application exposure to turf for children 1<2 years old. Note that for 9,10-anthraquinone, the child lifestage with the highest dietary exposure (all infants <1 year old) does not match the child lifestage with the highest residential exposure (children 1 to <2 years old). The lifestages selected for each residential post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs. This analysis provides a quantitative and qualitative basis for why children 1 to <2 years old are the representative lifestage for most residential post-application scenarios involving young children, as well as reasons why a residential assessment is not conducted for infants. For children, therefore, the 9,10-anthraquinone aggregate assessment only combines the residential exposure estimates for children 1 to <2 years old with the dietary exposure estimates for that same lifestage, children 1-2 years old.]

The non-cancer short-term aggregate MOE for children 1 to <2 years old was 2,200, which is not a risk estimate of concern (concern for MOEs ≤ LOC of 1,000).

Table 7.2. Non-Cancer Short-Term Aggregate Risk Calculations.

Population	Short- or Intermediate-Term Scenario						
	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food and Water Exposure[3] mg/kg/day	Residential Exposure mg/kg/day[4]	Total Exposure mg/kg/day[5]	Aggregate MOE (food, water, and residential)[6]
Children (1 to <2 years old)	44	1000	0.044	0.000086	0.0199	0.01999	2,200

[1] Child LOC = 1000 (10X for interspecies extrapolation, 10X for intraspecies variation, 10X for FQPA SF (LOAEL to NOAEL extrapolation).
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC.
[3] Source of average food and water exposure used in aggregate assessment (Table 5.4.6.1). For children, the dietary exposure estimate for Children 1 to <2 years old was used.
[4] Residential Exposure = [Oral exposure + Dermal exposure + Inhalation Exposure]. Source of residential exposure values used in non-cancer aggregate assessment (Table 6.3.1).
[5] Total Exposure = Avg Food & Water Exposure + Residential Exposure).
[6] Aggregate MOE = [NOAEL/(Avg Food & Water Exposure + Residential Exposure)].

7.3 Intermediate-Term Aggregate Risk

Intermediate-term aggregate assessments include exposures that will occur from thirty days to six months. There are no residential scenarios which are expected to be intermediate-term.

7.4 Chronic Aggregate Risk

Chronic or long-term aggregate assessments include exposures that will exceed six months. The chronic risk estimates include exposure to residues of 9,10-anthraquinone in food and drinking water, and do not include dermal, inhalation or incidental oral exposures because long-term exposures are not expected from the current use pattern. The chronic non-cancer risk estimates for adults, resulting from exposure to 9,10-anthraquinone in food and drinking water are below EPA's level of concern; therefore, the chronic non-cancer aggregate risks are not of concern. The general U.S. population and all population subgroups use <1% of the cPAD. See Section 5.4.4 and Table 5.4.6.1 for a detailed discussion of the chronic non-cancer dietary assessment.

7.5 Cancer Aggregate Risk

For the cancer aggregate assessment, the recommended residential exposure is dermal exposure to adults from post-application exposure to turf. The cancer aggregate risk is calculated using a linear slope factor (Q_1*) of $6x10^{-2}$ $(mg/kg/day)^{-1}$ multiplied by the sum of the residential LADD and dietary exposure (for adults 20-49 years old, the most highly exposed adult population subgroup) estimates. The cancer aggregate risk estimate is $2x10^{-4}$.

Table 7.5. Aggregate Cancer Risk Estimates.				
Population	**Cancer Slope Factor (Q_1*)**	**Food and Water Exposure (mg/kg/day)[1]**	**Residential Exposure (LADD - mg/kg/day[2]**	**Aggregate Cancer Risk (food, water, residential)**
Most Highly-exposed Adult Population Subgroup (Adults 20-49 years old)	$6x10^{-2}$ (mg/kg/day)$^{-1}$	0.000047	0.0028	$2x10^{-4}$

[1] Source of average food and water exposure used in aggregate assessment (Table 5.4.6.1). The cancer dietary exposure estimate for adults 20-49 years old was used.
[2] Residential exposure values used in aggregate assessment can be found in Table 6.3.2.
[3] Aggregate Cancer Risk = (Q_1*) (Food & Water Exposure + LADD).

8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (*e.g.*, children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.[7] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

One 9,10-anthraquinone product label has registered residential turf uses (i.e., home lawns), thus it was considered whether the risk assessment for that use may be considered protective of any type of exposure that would be associated with spray drift. If the maximum application rate on non-lawn turfgrass adjusted by the amount of drift expected is less than or equal to existing lawn turf application rates, the existing lawn turf assessment is considered protective of spray drift exposure. Note that this assumes similar formulations are being applied to the non-lawn turfgrass and the residential turf (i.e., if a granular product is registered for use on residential turf, the scenarios assessed for that use may not be protective of liquid applications made to agricultural crops). The currently registered maximum single application rate of 9,10-anthraquinone for non-lawn turfgrass is 1.03 lbs ai/A. The highest degree of spray drift noted for any application method immediately adjacent to a treated field (Tier 1 output from the aerial

[7] This approach is consistent with the requirements of the EPA's Worker Protection Standard which, when included on all labels, precludes direct exposure pathways.

application using fine to medium spray quality) results in a deposition fraction of 0.26 of the application rate. A quantitative spray drift assessment for 9,10-anthraquinone is not required because the maximum application rate to a non-lawn turfgrass target site multiplied by the adjustment factor for drift of 0.26 is less than the maximum direct spray residential lawn turf application rate (1.03 lbs ai/A)[8] for any 9,10-anthraquinone products. The lawn turf post-application non-cancer MOEs have been previously assessed, are based on the revised SOPs for Residential Exposure Assessment, and are not of concern (i.e., see above in Section 6.2).

9.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from FIFRA Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[9]. The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (*Human Health Bystander Screening Level Analysis: Volatilization of Conventional Pesticides*[10]). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for 9,10-anthraquinone.

10.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to 9,10-anthraquinone and any other substances and 9,10-anthraquinone does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that 9,10-anthraquinone has a common mechanism of toxicity with other substances. In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[11] and conducting cumulative risk assessments (CRA)[12]. During Registration Review, the Agency will utilize this framework to determine if the available toxicological data for 9,10-anthraquinone suggests a candidate CMG may be established with

[8] 1.03 lb ai/A x 0.26 ≤ 1.03 lb ai/A

[9] http://archive.epa.gov/scipoly/sap/meetings/web/pdf/120309meetingminutes.pdf

[10] https://www.regulations.gov/document/EPA-HQ-OPP-2014-0219-0002

[11] *Guidance For Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999)*

[12] *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity (USEPA, 2002)*

other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

11.0 Occupational Exposure/Risk Characterization

11.1 Short-/Intermediate-Term/Cancer Occupational Handler Exposure and Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the registered uses. The quantitative exposure/risk assessment developed for occupational handlers is based on the scenarios listed in Tables 11.1.1 to 11.1.3.

Occupational Handler Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis.

Application Rate:
Maximum registered single application rates for occupational handler scenarios can be found in Table 3.3 and were used in the cancer assessments for 9,10-anthraquinone.

Unit Exposures: It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include Pesticide Handlers Exposure Database (PHED) 1.1, the Agricultural Handler Exposure Task Force (AHETF) database, the Outdoor Residential Exposure Task Force (ORETF) database, the Science Advisory Council for Exposure (ExpoSAC) Policy 14.1 (SOP for Seed Treatment), or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures," are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table,[13]" which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[14].

[13] Available: https://www.epa.gov/sites/production/files/2020-03/documents/opp-hed-pesticide-handler-surrogate-unit-exposure-table-march-2020.pdf
[14] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

Area Treated or Amount Handled for Turfgrass Uses: Based on ExpoSAC Policy 9.2, the amount treated or handled per day for turfgrass uses was assumed to be:

- 5 acres for groundboom treatments to landscaping turf (e.g., lawns, parks, sports fields)
- 40 acres for groundboom treatments to golf course turf
- 5 acres for mechanically pressurized handgun treatments to landscaping turf (e.g., lawns, parks, sports fields) and golf course turf
- 40 gallons handled for manually pressurized handwand and backpack equipment treatments to landscaping turf (e.g., lawns, parks, sports fields)

Amount of Seed Treated in a Commercial Seed Treatment Facility: Based on HED ExpoSAC Policy 15.2 (Table 2.1.1), the amount of seed treated per day, using the short-term duration amounts, which would be protective of intermediate-term amounts, was assumed to be:

- 339,500 lbs for sweet and field corn seeds
- 302,500 lbs for rice seeds

Amount of Seed Treated and Planted for On-Farm Seed Treatment: Based on HED ExpoSAC Policy 15.2 (Table 2.2.1), the amount of seed treated and planted per day was assumed to be:

- 8,050,000 seeds for field corn
- 4,779,120 seeds for sweet corn

Amount of Seed Planted: Based on HED ExpoSAC Policy 15.2 (Table 3.1), the amount planted per day is detailed below:

- 8,050,000 seeds for field corn
- 4,779,120 seeds for sweet corn
- 487,672,000 seeds for rice
- 249,600,000 seeds for rice (Way 2018a)[15]

Exposure Duration:
HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by many things, including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site. For most agricultural uses, it is reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region).

For 9,10-anthraquinone, based on the registered uses, short- and intermediate-term exposures are expected. Although commercial seed treatment facilities can operate year-round, long-term exposure durations are not expected as it is unlikely that any one active ingredient would be used every day for the entire treating season.

[15] Way, M.O. 2018a. Professor of Entomology at Texas A & M University. Comments supplied via email in response to questions submitted to USDA-OPMP about neonicotinoid use in rice, email dated 3/02/2018.

Personal Protective Equipment: Estimates of inhalation exposure were calculated for various levels of PPE. Results are presented for "baseline," defined as a single layer of clothing consisting of a long-sleeved shirt, long pants, shoes plus socks, no protective gloves, and no respirator, as well as baseline with various levels of PPE as necessary (e.g., respirator). The 9,10-anthraquinone product labels direct handlers to wear baseline attire, chemical-resistant gloves, protective goggles, and a PF10 respirator. Workers handling treated seed must wear baseline attire and chemical-resistant gloves.

Days per Year of Exposure:
To assess cancer risk, it is assumed that private growers would be exposed 10 days per year and commercial applicators would be exposed 30 days per year. The term "private grower" means that the grower or one of the workers would apply the pesticides to land owned or operated by the grower. Commercial applicators means the applicators are completing multiple applications for multiple clients.

For seed treatment uses, the private and commercial growers are analogous to on-farm and commercial seed treatment uses. HED's default days per year for on-farm seed treatments is 10 days and for commercial seed treatments is 30 days. Also presented in this document are cancer risk estimates based on alternate days per year of exposure provided by registrant submissions of survey data. For commercial seed treatment uses, 14 days of exposure per year is presented and for commercial seed planting, 8 days of exposure per year is presented based on the average treating period duration for 9,10-anthraquinone. For the on-farm hopper box seed treatment uses, 2 days of exposure per year was presented based on the smaller size of farms that use this product and the types of equipment used[16].

Years per Lifetime of Exposure: It is assumed that handlers would be exposed for 35 years out of a 78-year lifespan.

Lifetime Expectancy: Life expectancy values are from the Exposure Factors Handbook 2011 Edition Table 18-1 (U.S. EPA, 2011). The table shows that the overall life expectancy is 78 years based on life expectancy data from 2007. In 2007, the average life expectancy for males was 75 years and 80 years for females. Based on the available data, the recommended value for use in cancer risk assessments is 78 years.

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations
The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in Appendix A of the ORE document that supports this risk assessment (B. Van Deusen, D462829, 3/08/2022).

[16] Lawrence, D. et al, MRID 49581901, 3/4/2015, Survey on 9,10-anthraquinone Seed Treatment Use Data and Response to EPA's "9, 10-anthraquinone Revised Occupational and Residential Exposure Assessment of Section 3, 18, and 24(c) uses as Bird repellent on Turf, Nurseries, Landfills/Dumpsite, Building Surfaces, and Rice/Corn Seed Treatment"

Combining Exposures/Risk Estimates:
Occupational handler dermal and inhalation exposures are anticipated from registered 9,10-anthraquinone uses, however there was no dermal POD selected. Therefore, only inhalation exposures have been quantitatively assessed and there are no additional routes to combine.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates
Tables 11.1.1 through 11.1.3 provide summaries of the estimated exposures and non-cancer risk estimates to occupational pesticide handlers for registered turfgrass and seed treatment uses of 9,10-anthraquinone. Occupational handler non-cancer risk estimates are based on inhalation exposure and are not of concern (i.e., MOEs ≥LOC; LOC = 1,000) at label-required PPE (i.e., PF10 respirator) with MOEs ranging from 1,100 to 3,100,000.

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Turf Uses of 9,10-Anthraquinone.							
Exposure Scenario	**Crop or Target**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Level of PPE or Engineering control**	**Maximum Application Rate[2]**	**Area Treated or Amount Handled Daily[3]**	**Inhalation**	
						Dose (mg/kg/day)[4]	**MOE[5] (LOC = 1,000)**
Mixer/Loader							
Liquid, Groundboom, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	0.219	No-R	1.03 lb ai/acre	5 acres	0.000014	3,100,000
Liquid, Groundboom, Broadcast	Golf course (fairways, tees, greens)	0.219	No-R	1.03 lb ai/acre	40 acres	0.00011	390,000
Applicator							
Spray (all starting formulations), Groundboom, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	0.34	No-R	1.03 lb ai/acre	5 acres	0.000022	2,000,000
Spray (all starting formulations), Groundboom, Broadcast	Golf course (fairways, tees, greens)	0.34	No-R	1.03 lb ai/acre	40 acres	0.00018	250,000
Mixer/Loader/Applicator							
Liquid, Backpack, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	69.1	No-R	0.172 lb ai/gallon solution	40 gallons solution	0.0059	7,400
Liquid, Backpack, Spot	Landscaping, turf (lawns, athletic fields, parks, etc.)	2.58	No-R	0.172 lb ai/gallon solution	40 gallons solution	0.00022	200,000
Liquid, Manually-pressurized Handwand, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	23.6	No-R	0.172 lb ai/gallon solution	40 gallons solution	0.002	22,000
Liquid, Mechanically-pressurized Handgun, Broadcast	Golf course (fairways, tees, greens)	1.9	No-R	1.03 lb ai/acre	5 acres	0.00012	360,000
Liquid, Mechanically-pressurized Handgun, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	1.9	No-R	1.03 lb ai/acre	5 acres	0.00012	360,000

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data); Level of PPE: No-R = No Respirator.

2 Based on registered label (Reg. No. 69969-7).

3 Exposure Science Advisory Council Policy #9.2.

4 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ BW (80 kg).5 Inhalation MOE = Inhalation NOAEL (44 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

Table 11.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Commercial Liquid Seed Treatment Uses of 9,10-Anthraquinone.					
Crop or Target	**Maximum Application Rate[1]**	**Seed Treated or Amount Planted Daily (lb seed)[2]**	**Inhalation Unit Exposure (µg/lb ai) or ((µg ai/hr)/(lb ai/lb seed))[3] for cleaners [Level of PPE]**	**Inhalation**	
				Dose (mg/kg/day)[4]	**MOE[5] (LOC = 1,000)**
Treating					
Corn (Field and Sweet)	0.00165 lb ai/lb seed	339,500	1.2 No-R	0.0084	5,200
Rice	0.0029 lb ai/lb seed	302,500	1.2 No-R	0.0131	3,400
Packaging					
Corn (Field and Sweet)	0.00165 lb ai/lb seed	339,500	3.6 No-R	0.0253	1,700
Rice	0.0029 lb ai/lb seed	302,500	3.6 No-R	0.0395	1,100
Cleaning					
Corn (Field and Sweet)	0.00165 lb ai/lb seed	339,500	106,000 No-R	0.00548	8,000
Rice	0.0029 lb ai/lb seed	302,500	106,000 No-R	0.00961	4,600
Loading/Planting					
Corn (Field)	1.2×10^{-6} lb ai/seed	8,050,000 seeds	66 No-R	0.00805	5,500
Corn (Sweet)	9.2×10^{-7} lb ai/seed	4,779,120 seeds		0.00363	12,000
Rice	1.9×10^{-7} lb ai/seed	487,672,000 seeds	6.6 PF10-R	0.00754	5,800
		249,600,000 seeds[6]	66 No-R	0.0385	1,100

1 Based on registered labels (EPA Reg. Nos. 69969-6 & 69969-7).
2 HED default for lb seed treated/planted per day from HED Science Advisory Council for Exposure Policy 15.2 (January 2022)
3 Unit Exposures from HED Science Advisory Council for Exposure Policy 14.1: Standard Operating Procedures for Seed Treatment (January 2022)
4 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/lb seed) × Amount Treated/Planted (lb seed) ÷ BW (80 kg).
5 Inhalation MOE = Inhalation NOAEL (44 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
6 Based on 80 lbs of rice planted per acre and 200 acres planted per day (Way, M.O. 2018).

Table 11.1.3. Occupational Handler Non-Cancer Exposure and Risk Estimates for On-Farm Hopper Box Dust Seed Treatment Uses of 9,10-Anthraquinone.					
Crop or Target	**Maximum Application Rate[1]**	**Amount Treated and Planted Daily (# seeds)[2]**	**Inhalation Unit Exposure (µg/lb ai)[3] [Level of PPE]**	**Inhalation**	
				Dose (mg/kg/day)[4]	**MOE[5] (LOC = 1,000)**
Treating & Planting					
Corn (Field)	3.6×10^{-6} lb ai/seed	8,050,000	63.3 PF10-R	0.0226	1,900
Corn (Sweet)	2.7×10^{-6} lb ai/seed	4,779,120		0.01	4,300

1 Based on registered 24(c) labels (e.g., EPA Reg. No. TX130002).
2 HED default for number of seeds treated/planted per day from HED Science Advisory Council for Exposure Policy 15.2 (January 2022)
3 Unit Exposures from HED Science Advisory Council for Exposure Policy 14: Standard Operating Procedures for Seed Treatment (January 2022)
4 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/lb seed) × Amount Treated (lb seed) ÷ BW (80 kg).
5 Inhalation MOE = Inhalation NOAEL (44 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

Although a non-cancer dermal risk assessment was not performed because a dermal endpoint was not selected, a dermal cancer exposure and risk assessment was performed because dermal exposure contributes to the overall cancer risk for 9,10-anthraquinone.

Occupational Handler Cancer Exposure and Risk Equations

Cancer risk estimates were calculated using a linear low-dose extrapolation approach in which a Lifetime Average Daily Dose (LADD) is first calculated and then compared with a Q_1* that has been calculated for 9,10-anthraquinone based on dose response data in the appropriate toxicology study (Q_1* = $6x10^{-2}$ $(mg/kg/day)^{-1}$). Absorbed average daily dose (ADD) levels were used as the basis for calculating the LADD values. For dermal exposures, a DAF of 4% was applied. Dermal and inhalation ADD values were first added together to obtain combined ADD values. LADD values were then calculated and multiplied by the Q_1* to obtain cancer risk estimates. The algorithms used to estimate the LADD and cancer risk for occupational handlers can be found in Appendix B of the ORE document that supports this risk assessment (B. Van Deusen, D462829, 3/08/2022).

Summary of Occupational Handler Cancer Exposure and Risk Estimates

Tables 11.1.4 to 11.1.7 provide summaries of the estimated cancer risk estimates to occupational pesticide handlers for registered turfgrass and seed treatment uses of 9,10-anthraquinone. Occupational handler cancer risk estimates range from 9×10^{-5} to 5×10^{-8} for private handlers and 2×10^{-4} to 1×10^{-7} for commercial handlers of various PPE combinations including utilizing seed treatment equipment while operators wear gloves and respirators.

Table 11.1.4. Occupational Handler Cancer Exposure and Risk Estimates for Turf Uses of 9,10-Anthraquinone.

Crop or Target	Exposure Scenario	Private Handler				Commercial Handler			
		LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]	LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]
		Dermal[1]	Inhalation[2]			Dermal[1]	Inhalation[2]		
Mixer/Loader[5]									
Landscaping, turf (lawns, athletic fields, parks, etc.)	Liquid, Groundboom, Broadcast	0.0000012	0.00000017	0.0000014	8E-08	0.0000036	0.00000052	0.0000041	3E-07
Golf course (fairways, tees, greens)	Liquid, Groundboom, Broadcast	0.0000095	0.0000014	0.000011	7E-07	0.000029	0.0000042	0.000033	2E-06
						0.000023 EC/No-G	0.00000021 EC/No-R	0.000023 EC/No-G, No-R	1E-06 EC/No-G, No-R
Applicator[5]									
Landscaping, turf (lawns, athletic fields, parks, etc.)	Spray (all starting formulations), Groundboom, Broadcast	0.00000051	0.00000027	0.00000078	5E-08	0.0000015	0.00000081	0.0000023	1E-07
Golf course (fairways, tees, greens)	Spray (all starting formulations), Groundboom, Broadcast	0.0000041	0.0000022	0.0000062	4E-07	0.000012	0.0000065	0.000019	1E-06
Mixer/Loader/Applicator[5]									
Landscaping, turf (lawns, athletic fields, parks, etc.)	Liquid, Backpack, Broadcast	0.0013 SL/G	0.0000073 PF10-R	0.0013 SL/G, PF10-R	8E-05 SL/G, PF10-R	0.0039 SL/G	0.000022 PF10-R	0.0039 SL/G, PF10-R	2E-04 SL/G, PF10-R
		0.00071 DL/G		0.00072 DL/G, PF10-R	4E-05 DL/G, PF10-R	0.0021 DL/G		0.0022 DL/G, PF10-R	1E-04 DL/G, PF10-R
Landscaping, turf (lawns, athletic fields, parks, etc.)	Liquid, Backpack, Spot	0.00035 SL/G	0.00000027 PF10-R	0.00035 SL/G, PF10-R	2E-05 SL/G, PF10-R	0.0011 SL/G	0.00000082 PF10-R	0.0011 SL/G, PF10-R	6E-05 SL/G, PF10-R
		0.00018 DL/G		0.00018 DL/G, PF10-R	1E-05 DL/G, PF10-R	0.00052 DL/G		0.00052 DL/G, PF10-R	3E-05 DL/G, PF10-R
Landscaping, turf (lawns, athletic fields, parks, etc.)	Liquid, Manually-pressurized Handwand, Broadcast	0.000018 SL/G	0.0000025 PF10-R	0.000021 SL/G, PF10-R	1E-06 SL/G, PF10-R	0.000055 SL/G	0.0000075 PF10-R	0.000062 SL/G, PF10-R	4E-06 SL/G, PF10-R
		0.000016 DL/G		0.000018 DL/G, PF10-R	1E-06 DL/G, PF10-R	0.000047 DL/G		0.000054 DL/G, PF10-R	3E-06 DL/G, PF10-R

Table 11.1.4. Occupational Handler Cancer Exposure and Risk Estimates for Turf Uses of 9,10-Anthraquinone.

Crop or Target	Exposure Scenario	Private Handler				Commercial Handler			
		LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]	LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]
		Dermal[1]	Inhalation[2]			Dermal[1]	Inhalation[2]		
Golf course (fairways, tees, greens)	Liquid, Mechanically-pressurized Handgun, Broadcast	0.000028 SL/G	0.00000015 PF10-R	0.000028 SL/G, PF10-R	2E-06 SL/G, PF10-R	0.000084 SL/G	0.00000045 PF10-R	0.000084 SL/G, PF10-R	5E-06 SL/G, PF10-R
		0.000014 DL/G		0.000014 DL/G, PF10-R	9E-07 DL/G, PF10-R	0.000043 DL/G		0.000043 DL/G, PF10-R	3E-06 DL/G, PF10-R
Landscaping, turf (lawns, athletic fields, parks, etc.)	Liquid, Mechanically-pressurized Handgun, Broadcast	0.000028 SL/G		0.000028 SL/G, PF10-R	2E-06 SL/G, PF10-R	0.000084 SL/G		0.000084 SL/G, PF10-R	5E-06 SL/G, PF10-R
		0.000014 DL/G		0.000014 DL/G, PF10-R	9E-07 DL/G, PF10-R	0.000043 DL/G		0.000043 DL/G, PF10-R	3E-06 DL/G, PF10-R

1 Dermal LADD (mg/kg/day) = Dermal dose (mg/kg/day) × [Days per year of exposure (10 or 30 days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (35 yrs) ÷ Lifetime expectancy (78 yrs)].
2 Inhalation LADD (mg/kg/day) = Inhalation Dose (mg/kg/day) × [Days per year of exposure (10 or 30 days/yr) / 365 days/year] × [Years per lifetime of exposure (35 yrs) ÷ Lifetime expectancy (78 yrs)].
3 Total LADD (mg/kg/day) = Dermal LADD (mg/kg/day) + Inhalation LADD (mg/kg/day).
4 Cancer risk estimates = Total LADD × Q_1^*, where $Q_1^* = 6x10^{-2}$ $(mg/kg/day)^{-1}$
5 PPE = SL/G, No-R except where otherwise noted

Table 11.1.5. Occupational Handler Cancer Exposure and Risk Estimates for Commercial Seed Treatment Uses of 9,10-Anthraquinone.									
Crop or Target	Exposure Scenario	Commercial Handler 14 Days of Exposure per Year				Commercial Handler 30 Days of Exposure per Year			
		LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]	LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]
		Dermal[1]	Inhalation[2]			Dermal[1]	Inhalation[2]		
Treating (SL/G, PF10-R)									
Corn (Field and Sweet)	Liquid Commercial Seed Treatment	0.00025	0.000015	0.00026	$2x10^{-5}$	0.00053	0.000031	0.00056	$3x10^{-5}$
Rice		0.00039	0.000023	0.00041	$2x10^{-5}$	0.00083	0.000048	0.00088	$5x10^{-5}$
Treating (DL/G, PF10-R)									
Corn (Field and Sweet)	Liquid Commercial Seed Treatment	0.0002	0.000015	0.00022	$1x10^{-5}$	0.00044	0.000031	0.00047	$3x10^{-5}$
Rice		0.00032	0.000023	0.00034	$2x10^{-5}$	0.00068	0.000048	0.00073	$4x10^{-5}$
Packaging (SL/G, PF10-R)									
Corn (Field and Sweet)	Liquid Commercial Seed Treatment	0.000082	0.000044	0.00013	$8x10^{-6}$	0.00018	0.000031	0.00027	$2x10^{-5}$
Rice		0.00013	0.000068	0.0002	$1x10^{-5}$	0.00027	0.00015	0.00042	$3x10^{-5}$
Packaging (DL/G, PF10-R)									
Corn (Field and Sweet)	Liquid Commercial Seed Treatment	0.000063	0.000044	0.00011	$6x10^{-6}$	0.00014	0.000031	0.00023	$1x10^{-5}$
Rice		0.0001	0.000068	0.00017	$1x10^{-5}$	0.00021	0.00015	0.00036	$2x10^{-5}$
Cleaning (SL/G, PF10-R)									
Corn (Field and Sweet)	Liquid Commercial Seed Treatment	0.00083	0.0000094	0.00084	$5x10^{-5}$	0.0018	0.00002	0.0018	$1x10^{-4}$
Rice		0.0015	0.000017	0.0015	$9x10^{-5}$	0.0031	0.000035	0.0032	$6x10^{-5}$
Cleaning (DL/G, PF10-R)									
Corn (Field and Sweet)	Liquid Commercial Seed Treatment	0.00075	0.0000094	0.00076	$5x10^{-5}$	0.0016	0.00002	0.0016	$1x10^{-4}$
Rice		0.0013	0.000017	0.0013	$8x10^{-5}$	0.0028	0.000035	0.0029	$6x10^{-5}$

1 Dermal LADD (mg/kg/day) = Dermal dose (mg/kg/day) × [Days per year of exposure (14 or 30 days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (35 yrs) ÷ Lifetime expectancy (78 yrs)].
2 Inhalation LADD (mg/kg/day) = Inhalation Dose (mg/kg/day) × [Days per year of exposure (14 or 30 days/yr) / 365 days/year] × [Years per lifetime of exposure (35 yrs) ÷ Lifetime expectancy (78 yrs)].
3 Total LADD (mg/kg/day) = Dermal LADD (mg/kg/day) + Inhalation LADD (mg/kg/day).
4 Cancer risk estimates = Total LADD × Q_1^*, where $Q_1^* = 6x10^{-2}$ $(mg/kg/day)^{-1}$

Table 11.1.6. Occupational Handler Cancer Exposure and Risk Estimates for On-Farm Seed Treatment Uses of 9,10-Anthraquinone.

Crop or Target	Exposure Scenario	On-Farm Hopper Box 2 Days of Exposure				On-Farm Hopper Box 10 Days of Exposure			
		LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]	LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]
		Dermal[1]	Inhalation[2]			Dermal[1]	Inhalation[2]		
Treating & Planting (SL/G, PF10-R)									
Corn (Field)	Dust Hopper Box Seed Treatment	0.00027	0.000056	0.00033	$2x10^{-5}$	0.0013	0.00028	0.0016	$1x10^{-4}$
Corn (Sweet)		0.00012	0.000025	0.00015	$9x10^{-6}$	0.0006	0.00013	0.00073	$4x10^{-5}$
Treating & Planting (DL/G, PF10-R)									
Corn (Field)	Dust Hopper Box Seed Treatment	0.0002	0.000056	0.00025	$2x10^{-5}$	0.00098	0.00028	0.0013	$8x10^{-5}$
Corn (Sweet)		0.000088	0.000025	0.00011	$7x10^{-6}$	0.00044	0.00013	0.00056	$3x10^{-5}$

1 Dermal LADD (mg/kg/day) = Dermal dose (mg/kg/day) × [Days per year of exposure (2 or 10 days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (35 yrs) ÷ Lifetime expectancy (78 yrs)].

2 Inhalation LADD (mg/kg/day) = Inhalation Dose (mg/kg/day) × [Days per year of exposure (2 or 10 days/yr) / 365 days/year] × [Years per lifetime of exposure (35 yrs) ÷ Lifetime expectancy (78 yrs)].

3 Total LADD (mg/kg/day) = Dermal LADD (mg/kg/day) + Inhalation LADD (mg/kg/day).

4 Cancer risk estimates = Total LADD × Q_1^*, where $Q_1^* = 6x10^{-2}$ $(mg/kg/day)^{-1}$

Table 11.1.7. Occupational Handler Cancer Exposure and Risk Estimates for Seed Planter Uses of 9,10-Anthraquinone.									
Crop or Target	Exposure Scenario	Commercial Planter 8 Days of Exposure per Year				Commercial Planter 30 Days of Exposure per Year			
		LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]	LADD (mg/kg/day)		Total LADD[3]	Cancer Risk Estimate[4]
		Dermal[1]	Inhalation[2]			Dermal[1]	Inhalation[2]		
Loading/Planting (SL/G, PF10-R)									
Corn (Field)	Liquid Commercial Seed Treatment	0.000038	0.0000079	0.000046	$3x10^{-6}$	0.00014	0.00003	0.00017	$1x10^{-5}$
Corn (Sweet)	Liquid Commercial Seed Treatment	0.000017	0.0000036	0.000021	$1x10^{-6}$	0.000065	0.000013	0.000078	$5x10^{-6}$
Rice	Liquid Commercial Seed Treatment	0.00036	0.000074	0.00043	$3x10^{-5}$	0.0013	0.00028	0.0016	$1x10^{-4}$
	Liquid Commercial Seed Treatment[5]	0.00018	0.000038	0.00022	$1x10^{-5}$	0.00068	0.00014	0.00082	$5x10^{-5}$
Loading/Planting (DL/G, PF10-R)									
Corn (Field)	Liquid Commercial Seed Treatment	0.000026	0.0000079	0.000033	$2x10^{-6}$	0.000096	0.00003	0.00013	$8x10^{-6}$
Corn (Sweet)	Liquid Commercial Seed Treatment	0.000012	0.0000036	0.000015	$9x10^{-7}$	0.000043	0.000013	0.000056	$3x10^{-6}$
Rice	Liquid Commercial Seed Treatment	0.00024	0.000074	0.00031	$2x10^{-5}$	0.00089	0.00028	0.0012	$7x10^{-5}$
	Liquid Commercial Seed Treatment[5]	0.00012	0.000038	0.00016	$9x10^{-6}$	0.00045	0.00014	0.00059	$4x10^{-5}$

1 Dermal LADD (mg/kg/day) = Dermal dose (mg/kg/day) × [Days per year of exposure (10 or 30 days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (35 yrs) ÷ Lifetime expectancy (78 yrs)].
2 Inhalation LADD (mg/kg/day) = Inhalation Dose (mg/kg/day) × [Days per year of exposure (10 or 30 days/yr) / 365 days/year] × [Years per lifetime of exposure (35 yrs) ÷ Lifetime expectancy (78 yrs)].
3 Total LADD (mg/kg/day) = Dermal LADD (mg/kg/day) + Inhalation LADD (mg/kg/day).
4 Cancer risk estimates = Total LADD × Q_1^*, where $Q_1^* = 6x10^{-2}$ $(mg/kg/day)^{-1}$.
5 Based on 80 lbs of rice planted per acre and 200 acres planted per day (Way, M.O. 2018).

11.2 Short-Term/Cancer Post-Application Exposure and Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

Occupational post-application dermal exposure is anticipated from registered 9,10-anthraquinone turfgrass uses, however there was no dermal POD selected. Therefore, occupational post-application non-cancer dermal exposures have not been quantitatively assessed.

Although a non-cancer post-application dermal risk assessment was not performed, a dermal cancer exposure and risk assessment was performed because dermal exposure contributes to the overall cancer risk for 9,10-anthraquinone.

11.2.1 Dermal Post-Application Risk

Occupational post-application dermal exposures from seed treatment uses are not anticipated. The potential for post-application exposures following the planting of treated seeds is unlikely because sustained levels of contact with treated seed after it has been placed in the soil or other planting media would not be expected because no routine cultural practice required for the production of agricultural commodities involves such an activity, as defined in the no/low contact criteria in the Worker Protection Standard (WPS).

Occupational Post-application Dermal Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the occupational post-application cancer risk assessments. Each assumption and factor is detailed below on an individual basis.

Transfer Coefficients: It is the policy of HED to use the best available data to assess post-application exposure. Sources of generic post-application data, used as surrogate data in the absence of chemical-specific data, are derived from ARTF exposure monitoring studies, and, as proprietary data, are subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting post-application exposure that are used in this assessment, known as "transfer coefficients," are presented in the ExpoSAC Policy 3[17]" which, along with additional information about the ARTF data, can be found at the Agency website[18]. Table 11.2.1.1 provides a summary of the anticipated post-application activities and associated transfer coefficients for the proposed crops/use sites.

[17] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data
[18] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

Table 11.2.1.1. Anticipated Post-Application Activities and Dermal Transfer Coefficients.			
Proposed Crops	**Policy Crop Group Category**	**Transfer Coefficients (cm^2/hr)**	**Activities**
Golf Course	Turf	3,700	Maintenance
		2,500	Maintenance (Greens Only)

Application Rate: Maximum single application rates for occupational handler scenarios can be found in Table 3.3. Typical application rates were not available so maximum registered application rates were used in the cancer assessments for 9,10-anthraquinone.

Exposure Time: The average occupational workday is assumed to be 8 hours.

Turf Transferable Residue (TTR) Data: A chemical-specific TTR study ("Determination of Turf Transferable Residues (TTR) on Turf Treated with FlightControl Plus," EPA MRID 48639805) was submitted for 9,10-anthraquinone. The TTR study was reviewed and found to be acceptable for risk assessment (A. Rivera-Lupiáñez, D396314, 10/12/2012). The data from this study were used to assess cancer post-application exposure from the registered golf course turf uses of 9,10-anthraquinone. Further details can be found in section 6.2 above and in Appendix C of the ORE document that supports this risk assessment (B. Van Deusen, D462829, 3/08/2022).

Days per Year of Exposure:
To assess cancer risk, it is assumed that occupational workers performing maintenance activities on golf course turf would be exposed 30 days per year.

Years per Lifetime of Exposure: HED assumes that post-application workers would be exposed for 35 years out of a 78-year lifespan.

Lifetime Expectancy: Based on available data from EPA's Exposure Factors Handbook 2011 Edition, the recommended lifespan for use in cancer risk assessments is 78 years. Life expectancy values are derived from the Exposure Factors Handbook 2011 Edition Table 18-1 (U.S. EPA, 2011). The table shows that the overall life expectancy is 78 years based on life expectancy data from 2007. In 2007, the average life expectancy for males was 75 years and 80 years for females.

Occupational Post-application Cancer Dermal Exposure and Risk Equations
As was done for occupational handlers, post-application cancer risk estimates were calculated using a linear low-dose extrapolation approach in which a LADD is first calculated applying a DAF of 4% and then multiplied by a Q_1^* that has been calculated for 9,10-anthraquinone based on dose response data in the appropriate toxicology study ($Q_1^* = 6x10^{-2}$ $(mg/kg/day)^{-1}$). Two LADD values have been presented to represent different residue values. The day 0 residue value is presented as well as a 14-day average residue for the cancer assessments to represent an average residue value based on the registered 14-day re-treatment interval. The algorithms used to estimate the LADD and cancer risk for occupational workers can be found in Appendix B of the ORE document that supports this risk assessment (B. Van Deusen, D462829, 3/08/2022).

Occupational Post-application Cancer Dermal Risk Estimates

Table 11.2.1.2 provides a summary of the estimated cancer dermal risk estimates to occupational workers performing maintenance activities on golf course turfgrass previously treated with 9,10-anthraquinone. Occupational post-application cancer risk estimates range from 5×10^{-6} to 3×10^{-6}.

Table 11.2.1.2. Occupational Post-Application Cancer Exposure and Risk Estimates for 9,10-Anthraquinone.

Crop Grouping/Crop	Activity	Days After Treatment	Dermal LADD (mg/kg/day)[1]	Cancer Risk Estimate[2]
Golf Course Turf	Maintenance	0	$8x10^{-5}$	$5x10^{-6}$
		14-day average residue[3]	$6.1x10^{-5}$	$4x10^{-6}$
	Maintenance (Greens Only)	0	$5.4x10^{-5}$	$3x10^{-6}$
		14-day average residue[3]	$4.1x10^{-5}$	$3x10^{-6}$

1 Dermal LADD (mg/kg/day) = Dermal dose (mg/kg/day) × [Days per year of exposure (30 days/yr) ÷ 365 days/year] × [Years per lifetime of exposure (35 yrs) ÷ Lifetime expectancy (78 yrs)].

2 Cancer risk estimate = Dermal LADD (mg/kg/day) × Q_1^*, where $Q_1^* = 6x10^{-2}$ (mg/kg/day)$^{-1}$.

3 14-day average residue calculated based on 14-day re-treatment interval.

Restricted Entry Interval

9,10-anthraquinone is classified as Toxicity Category IV via the dermal route and for skin irritation potential. It is not a skin sensitizer. A non-cancer dermal post-application risk assessment was not performed as there was no dermal POD selected. 9,10-anthraquinone is classified as "Likely to be Carcinogenic to Humans." Under 40 CFR 156.208 (c) (2), ai's classified as Acute III or IV for acute dermal, eye irritation and primary skin irritation are assigned a 12-hour REI. The REI listed on applicable registered labels (i.e., on-farm seed treatment uses) is 4-hours.

Based on the acute toxicity categories for 9,10-anthraquinone, the Worker Protection Standard (WPS) Interim Restricted Entry Interval (REI) for 9,10-anthraquinone would be 12-hours. REIs may be further reduced if certain criteria are met in accordance with the Pesticide Registration (PR) Notice 95-3 [Reduction of WPS Interim REIs for Certain Low Risk Pesticides][19]. In PR Notice 95-3, there are a set of criteria listed for the active ingredient that must be met for chemicals to be eligible for a reduced REI. These criteria include:

1. The active ingredient is in Toxicity Category III or IV based upon data for acute dermal toxicity, acute inhalation toxicity, primary skin irritation, and primary eye irritation. Acute oral toxicity data were used if no acute dermal data were available. If EPA lacked data on primary skin irritation, acute inhalation, or primary eye irritation of the active ingredient, the Agency reviewed data on that endpoint for similar active ingredients (analogs), and excluded such active ingredients from consideration for the reduced REI, if the analog is in Toxicity Category I or II for that endpoint.
2. The active ingredient is not a dermal sensitizer (or in the case of biochemical and

[19] Available: https://www.epa.gov/pesticide-registration/prn-95-3-reduction-worker-protection-standard-wps-interim-restricted-entry

microbial active ingredients, no known reports of hypersensitivity exist).
3. The active ingredient is not a cholinesterase inhibitor (e.g., N-Methyl carbamate and Organophosphate) as these chemicals are known to cause large numbers of pesticide poisonings and have the potential for serious neurological effects.
4. No known reproductive, developmental, carcinogenic, or neurotoxic effects have been associated with the active ingredient. If active ingredients did not have data available for these chronic health effects, EPA considered data on appropriate chemical and biological analogs. Active ingredients that have been classified as carcinogenic in Category B (probable human carcinogen) or Category C with a potency factor, Q* (possible human carcinogen, for which quantification of potential risk is considered appropriate), or are scheduled for HED's Cancer Peer Review process, were omitted from consideration.
5. EPA does not possess incident information (illness or injury reports) that are "definitely" or "probably" related to post-application exposures to the active ingredient.

EPA Cancer Classifications were most recently updated in 2005[20], which differs in terminology as referenced above (i.e., Category B or Category C) and due to that change, the current classifications that would result in omission for reduced REI consideration are "Carcinogenic to Humans" and "Likely to be Carcinogenic to Humans," with a carcinogenic potency factor (Q*). 9,10-anthraquinone is currently classified as "Likely to be Carcinogenic to Humans" and, therefore, does not meet the criteria for chemicals to be eligible for a reduced REI.

Upon review of the criteria for the active ingredient only, it appears that 9,10-anthraquinone does not meet the criteria in PRN 95-3 that allows for a 4-hour REI. **Note**: *The PR Notice also includes similar criteria for the end-use product. These criteria have not been evaluated by HED.* Based solely on the active ingredient criteria, HED would not recommend for a reduction of the REI for 9,10-anthraquinone and is recommending that the REI be revised on the labels to address those concerns.

11.2.2 Inhalation Post-Application Risk

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from FIFRA Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[21]. The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (*Human Health Bystander Screening Level Analysis: Volatilization of Conventional Pesticides*[22]). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for 9,10-anthraquinone.

[20] Guidelines for Carcinogen Risk Assessment
[21] http://archive.epa.gov/scipoly/sap/meetings/web/pdf/120309meetingminutes.pdf
[22] https://www.regulations.gov/document/EPA-HQ-OPP-2014-0219-0002

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments.

Although a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios.

For seed treatment, a post-application inhalation exposure assessment is not required as exposure is expected to be negligible. Seed treatment assessments provide quantitative inhalation exposure assessments for seed treaters and planters. It is expected that these exposure estimates would be protective of any potential low-level post-application inhalation exposure that could result from these types of applications.

12.0 Incident and Epidemiological Data Review

Both OPP Incident Data System (IDS) and the Centers for Disease Control and Prevention/ National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR) databases were consulted for pesticide incident data on 9,10-anthraquinone (S. Recore, D462830, 7/20/2021). The purpose of the database search is to identify potential patterns in the frequency and severity of the health effects attributed to 9,10-anthraquinone exposure. Based on the low frequency and severity of anthraquinone incident cases reported to IDS and NIOSH SENSOR-Pesticides, there does not appear to be a concern at this time. The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be included in the risk assessment.
No 9,10-anthraquinone incidents were reported to either Main IDS or Aggregate IDS for the five years from January 1, 2016 to July 14, 2021. A query of SENSOR-Pesticides from 1998-2017 identified no cases involving anthraquinone. The Agricultural Health Study (AHS) is a federally-funded study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the US National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), CDC's NIOSH, and the US EPA. Anthraquinone is not included in the AHS, and therefore this study does not provide information for this report. There does not appear to be a concern at this time because no 9,10-anthraquinone incidents were reported to either IDS or SENSOR-Pesticides.

13.0 References

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Appendix A. Toxicology Profile, Literature Search, and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.500) for Food Use for anthraquinone are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Study		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Acute Eye Irritation	yes	yes
870.2500	Acute Dermal Irritation	yes	yes
870.2600	Skin Sensitization	yes	yes
870.3100	90-Day Oral Toxicity in Rodents	yes	yes
870.3150	90-Day Oral Toxicity in Nonrodents	yes	waived[1]
870.3200	21/28-Day Dermal Toxicity	yes	yes
870.3250	90-Day Dermal Toxicity	yes	---[4]
870.3465	90-Day Inhalation Toxicity	yes	waived[1]
870.3700a	Prenatal Developmental Toxicity (rodent)	yes	yes
870.3700b	Prenatal Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction and Fertility Effects	yes	waived[2]
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	no	--
870.4200a	Carcinogenicity (rat)	yes	yes
870.4200b	Carcinogenicity (mouse)	yes	yes
870.4300	Combined Chronic Toxicity/Carcinogenicity	yes	yes
870.5100	Mutagenicity—Bacterial Reverse Mutation Test	yes	yes
870.5300	Mutagenicity—Mammalian Cell Gene Mutation Test	yes	yes
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	waived[2]
870.6200b	90-Day Neurotoxicity Screening Battery (rat)	yes	waived[2]
870.6300	Developmental Neurotoxicity	--	--
870.7485	Metabolism and Pharmacokinetics	yes	yes
870.7600	Dermal Penetration	no	no
870.7800	Immunotoxicity	yes	yes
Non-guideline Special Study			
	Comparative Thyroid Assay	--	Waived[3]

[1] Waived by HASPOC: K. Yozzo, TXR 0057823, 1/29/2019
[2] Waived by HASPOC: M. Zampariello, TXR 0058067, 1/12/2021
[3] Waived by HASPOC: H. DeLeon, TXR 0058198, 7/29/2021
[4] Requirement satisfied by submission of 28-day dermal study in rats

A.2 Toxicity Profiles

Table A.2.1 Acute Toxicity Profile – 9,10-anthraquinone Technical[1]				
Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute Oral (rat)	44496109	LD_{50} > 5143 mg/kg (M & F)	IV
870.1200	Acute Dermal (rabbit)	44496110	LD_{50} > 5000 mg/kg (M & F)	IV
870.1300	Acute Inhalation (rat)	44496112	LC_{50} > 2.14 mg/L (M & F)	IV
870.2400	Primary Eye Irritation (rabbit)	50965013	Minimally irritating	IV
870.2500	Primary Skin Irritation (rabbit)	50965014	Minimally irritating	IV
870.2600	Dermal Sensitization (mouse)	50965015	Not a dermal sensitizer (LLNA)	N/A

[1] B. Backus, TXR 5018163, D455561, 9/04/2020. For the acute oral, dermal and inhalation studies the purity of the test material was 99.2% and for the primary eye, dermal and dermal sensitization it was 97.1%.

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile - 9,10-Anthraquinone		
Guideline No./ Study Type	**MRID No. (year)/TXR No. and/or DP Barcode/ Classification/Doses**	**Results**
870.3100 90- Day oral toxicity (dietary) (Sprague Dawley rat)	MRID 48708301 (2011) D462832; TXR 0052851 Acceptable/Guideline 0, 500*, 2000, or 7500 ppm [*500 ppm reduced to 200 ppm (11/16 mg/kg/day, M/F) at week 5] M: 0, 40/11, 125, 495 mg/kg/day F: 0, 44/16, 150, 661 mg/kg/day	LOAEL = 44 mg/kg/day based on decreased body weight in females. [Note: After the low dose was decreased from 40 to 11 mg/kg/day in males and from 44 to 16 mg/kg/day in females beginning on week 5, the body weight decreases remained flat (i.e., no trend related increase over time (week 7 [↓8% males, ↓15% females] and week 13 [↓6% males, ↓13% females]). In females, the decreased body weight at weeks 7 and 13 of >10% was considered to be a carryover effect from the higher dose of 44 mg/kg/day rather than 16 mg/kg/day; therefore, the LOAEL was set at 44 mg/kg/day (the lowest dose originally tested), instead of 16 mg/kg/day. At the higher doses, the body weight decreases became greater over time. This effect was more pronounced in females.] NOAEL was not established.
NTP Study Non-Guideline 14-Week study (dietary) (F344 Rat)	MRID 48370301 NTP report (2005) D462832; TXR 0052851 Acceptable/Non-guideline 0, 1875, 3750, 7500, 15000, 30,000 ppm 0, 135, 275, 555, 1130, 2350 mg/kg/day, M/F	LOAEL = 275 mg/kg/day based on increased urinary N-acetyl-β-D-glucosaminidase (NAG) enzyme activity in females and thyroid follicular cell hypertrophy in both sexes. NOAEL= 135 mg/kg/day.

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile - 9,10-Anthraquinone		
Guideline No./ Study Type	**MRID No. (year)/TXR No. and/or DP Barcode/ Classification/Doses**	**Results**
NTP Study Non-Guideline 14-Week Mouse study (dietary)	MRID 48370301 NTP report (2005) D462832; TXR 0052851 Acceptable/Non-guideline 0, 1875, 3750, 7500, 15000, 30,000 ppm M: 0, 250, 500, 1050, 2150, 4300 mg/kg/day F: 0, 300, 640, 1260, 2600, 5300 mg/kg/day	LOAEL = 500/640 mg/kg/day, M/F (3750 ppm), based on increased liver weights (both sexes) and microscopic findings in the liver (centrilobular hypertrophy) in both sexes and urinary bladder (cytoplasmic alteration of the transitional epithelium) in males. NOAEL = 250/300 mg/kg/day, M/F
870.3150 90-Day Oral Toxicity in Nonrodents		Waived by HASPOC (K. Yozzo, TXR 0057823, 1/29/2019)
870.3200 28-Day dermal toxicity (Sprague Dawley rat)	MRID 48639801 (2011) D462832; TXR 0052851 Acceptable/ guideline 0, 100, 300, or 1000 mg/kg/day (M&F)	LOAEL = 1000 mg/kg/day (highest dose tested) based thyroid follicular cell hypertrophy in males and hepatocyte necrosis. NOAEL is 300 mg/kg/day
870.3465	90-Day Inhalation Toxicity	Waived by HASPOC (K. Yozzo, TXR 0057823, 1/29/2019)
870.3700a Prenatal developmental (gavage) (Sprague Dawley rat)	MRIDs 48639803 and 48639802 (2011) D462832; TXR 0052851 Acceptable/ guideline 0, 10, 50, or 150 mg/kg/day	Maternal LOAEL = 150 mg/kg/day, based on decreased body weight and food consumption. Maternal NOAEL = 50 mg/kg/day Developmental LOAEL = 150 mg/kg/day, based on decreased fetal weight (both sexes), litter weight, and placental weight. Developmental NOAEL = 50 mg/kg/day.
870.3700b Prenatal developmental (gavage) (rabbit)	MRID 50131501 (2017) Range finder 50131502 (2016) D462832; TXR 0052851 Acceptable/guideline 0, 25, 50, or 100 mg/kg/day	Maternal LOAEL = 50 mg/kg bw/day, based on increased mortality (20%), late abortions (gestation days 25 and 28), and clinical signs (decreased feces output and red urine). Maternal NOAEL = 25 mg/kg bw/day. Developmental LOAEL = 50 mg/kg/day based on late abortions. Developmental NOAEL = 25 mg/kg/day.
870.3800 Reproduction and Fertility Effects		Waived by HASPOC (M. Zampariello, TXR 0058067, 1/12/2021)

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile - 9,10-Anthraquinone		
Guideline No./ Study Type	**MRID No. (year)/TXR No. and/or DP Barcode/ Classification/Doses**	**Results**
NTP study Non-Guideline Carcinogenicity (F344 rat)	MRID 48370301 NTP report (2005) D462832; TXR 0052851 Acceptable/non-guideline 0, 469, 938, 1875, 3750 ppm Equivalent to: Male: 0, 20, 45, 95, 180 mg/kg/day Female: 0, 25, 50, 100, 200 mg/kg/day	LOAEL = 20/25 mg/kg/day, M/F, based on decreased body weight in females. kidney histopathological effects, including hyaline droplet accumulation, nephropathy, pigmentation, renal tubular hyperplasia, and mineralization of medulla in females and mineralization of medulla in males, as well as several liver histopathological effects, including cystic degeneration, inflammation, and eosinophilic and mixed-cell foci in both sexes, and cytoplasmic vacuolization in males. NOAEL was not established. From CARC: Kidney tumors in female rats are treatment related. [Urinary bladder transitional epithelial and kidney tumors in male rats are NOT treatment related. Thyroid tumors in female rats are NOT treatment-related]
NTP study Non-guideline Carcinogenicity (mouse)	MRID 48370301 NTP report (2005) D462832; TXR 0052851 Acceptable/ non-guideline 0, 833, 2500 or 7500 ppm Equivalent to: Male: 0, 90, 265, 825 mg/kg/day Female: 0, 80, 235 or 745 mg/kg/day	LOAEL = 90/80 mg/kg/day, based on microscopic findings in the liver (centrilobular hypertrophy). NOAEL was not established. From CARC: Liver tumors in male and female mice are treatment related. Also, thyroid follicular cell tumors in male and female mice are treatment related.
870.5100 *In vitro* Bacterial Reverse Gene Mutation (Ames Assay) *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 *Escherichia Coli strains (WP2uvrA/2 trials)*	MRID 44496117 (1997) (99.2% technical grade; Lot 64077) D462832; TXR 0052851 Acceptable/Guideline Range-Finder: 6.67-5000 µg Main: 500, 250, 125, 62.5, 31.3, and 15.7 µg/plate in both the presence (+) and absence (-) of metabolic activation (Aroclor-induced rat liver S9 mix).	Negative for induced mutant colonies over background in any strain in +/- S9.
870.5100 *In vitro* Bacterial Reverse Gene Mutation (Ames Assay) Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537	MRID 50345102 (2009) D463728; TXR 0058227 Acceptable/Guideline NTP AQ-OX (99.8% a.i., NTP lot #5893) AQ-OX is anthraquinone manufactured by oxidation of anthracene.	Positive. NTP AQ-OX caused a positive increase in the mean number of revertants/plate with strains TA98 +/-S9, TA100 -S9, and TA1537 +/-S9.

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile - 9,10-Anthraquinone		
Guideline No./ Study Type	**MRID No. (year)/TXR No. and/or DP Barcode/ Classification/Doses**	**Results**
Escherichia Coli strains (WP2uvrA/2 trials)	30, 60, 125, 250, 500, 1000 and 2000 µg/plate in the presence and absence of mammalian metabolic activation (Aroclor-induced rat liver S9)	
870.5100 *In vitro* Bacterial Reverse Gene Mutation (Ames Assay) Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 Escherichia Coli strains (WP2uvrA/2 trials)	MRID 50345103 (2009) D463728; TXR 0058227 Acceptable/Guideline NTP AQ-OX Pure (AQ-OX is anthraquinone manufactured by oxidation of anthracene) 30.0, 60.0, 125, 250, 500, 1000, and 2000 µg/plate were tested in both the presence and absence of mammalian metabolic activation (Aroclor-induced rat liver S9)	Negative. There was no evidence of induced mutant colonies over background in any strain in the presence or absence of S9 activation.
870.5100 *In vitro* Bacterial Reverse Gene Mutation (Ames Assay) Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 Escherichia Coli strains (WP2uvrA/2 trials)	MRID 50345104 (2009) D463728; TXR 0058227 Acceptable/Guideline AQ-FC (>99% ai) (AQ-FC is anthraquinone manufactured by Friedel Crafts method.) 30.0, 60.0, 125, 250, 500, 1000, and 2000 µg/plate were tested in both the presence and absence of mammalian metabolic activation (Aroclor-induced rat liver S9)	Negative. There was no evidence of induced mutant colonies over background in any strain in the presence or absence of S9 activation.
870.5100 *In vitro* Bacterial Reverse Gene Mutation (Ames Assay) Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537 Escherichia Coli strains (WP2uvrA/2 trials)	MRID 50345105 (2009) D463728; TXR 0058227 Acceptable/Guideline AQ-DA formed by the Diels-Alder process (99.4% ai) 30.0, 60.0, 125, 250, 500, 1000, and 2000 µg/plate	Negative. There was no evidence of induced mutant colonies over background in any strain in the presence or absence of S9 activation.
870.5100 *In vitro* Bacterial Reverse Gene Mutation (Ames Assay) Salmonella typhimurium strains TA98, TA100, TA1535, and	MRID 50345106 (2001) D463728; TXR 0058227 Acceptable/Guideline 2-OH-anthraquinone (metabolite of anthraquinone) (purified) Doses tested with Salmonella	Positive. Positive increases in the number of revertants/plate above vehicle control for strains TA100 and TA1537, both in the presence of S9 mix.

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile - 9,10-Anthraquinone		
Guideline No./ Study Type	**MRID No. (year)/TXR No. and/or DP Barcode/ Classification/Doses**	**Results**
TA1537 Escherichia Coli strains (WP2uvrA/2 trials)	strains: 0.333, 1.00, 3.33, 10.0, 33.3, and 100 µg/plate in the presence S9 mix and doses at 1.00, 3.33, 10.0, 33.3, 100, and 333 µg/plate without S9 mix in the plate incorporation procedure. The six doses tested with WP2uvrA were 3.33, 10.0, 33.3, 100, 333, 1000 µg/plate.	
870.5100 *In vitro* Bacterial Reverse Gene Mutation (Ames Assay) Salmonella typhimurium strains TA98, TA100, TA102, and TA1537	MRID 48370301 NTP Report (2005) D463729; TXR 0058228 Acceptable/Guideline Anthraquinone (97%): 33-2500 µg/plate Anthraquinone (100%): 100-10,000 µg/plate Anthraquinone (≥99%): 30-2000 µg/plate AQ-DA, AQ-FC: 30-10,000 µg/plate *Metabolites* 1-OH-AQ: 100-10,000 µg/plate 2-OH-AQ: 3.3-450 µg/plate *Impurities* 1-Nitroanthracene: 0.1-33 µg/plate 2-Nitroanthracene: 0.033-20 µg/plate 9-Nitroanthracene: 100-6667 µg/plate	Anthraquinone (97% pure): Positive in strains TA98 and TA100 +/-S9 Anthraquinone (100% pure): Negative in strains TA98, TA100, TA102 +/- S9 Anthraquinone (A07496, ≥99% pure): Negative in strains TA98, TA100, TA1537 +/-S9 Anthraquinone (A65343, Diels-Alder (DA), 99.4% pure): Negative in strains TA98 and TA100 +/-S9 Anthraquinone (A54984, Friedel-Crafts (FC), >99% pure): Negative in strains TA98 and TA100 +/-S9 Anthraquinone (A40147, Diels-Alder (DA), 99.4% pure): Positive in TA98 and TA100 +/-S9 <u>*Metabolites*</u> 1-Hydroxyanthraquinone: Negative in strains TA98, TA100, and TA102 +/-S9 2-Hydroxyanthraquinone: Positive in strain TA98 +/-S9 and negative in strain TA100 +/-S9 <u>*Impurities*</u> 1-Nitroanthracene: Positive in strains TA98 and TA100 +/-S9 2-Nitroanthracene: Positive in strains TA98 and TA100 +/-S9 9-Nitroanthracene: Positive in strains TA98 and TA100 +/-S9
870.5375 *In vitro* mammalian cell assay Mouse Lymphoma (L5178Y cells)	MRID 44496118 (1997) D462832; TXR 0052851 Anthraquinone (99.2%) 1.57, 3.13, 6.25, 12.50, 25.0, 37.5, 50.0 µg/mL in both the presence (+) and absence (-) of S9 mix.	Negative with and without S9 metabolic activation under the conditions of testing. Positive controls induced large increases in mutant frequency.

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile - 9,10-Anthraquinone		
Guideline No./ Study Type	**MRID No. (year)/TXR No. and/or DP Barcode/ Classification/Doses**	**Results**
870.5375 *In vitro* mammalian cell assay Chromosomal Aberrations in Chinese Hamster Ovary (CHO) cells	MRID 44496120 (1997) D462832; TXR 0052851 Anthraquinone (99.2%) Acceptable/Guideline 5.0, 12.5, 25.0, 37.5, 50.0 µg/mL with and/or without metabolic activation (Aroclor-induced rat liver S9)	Negative. There was no evidence of chromosome aberrations induced over background with and without metabolic activation.
870.5395 *In vivo* mammalian cytogenetics Mouse *(In vivo* Erythrocyte Micronucleus Assay)	MRID 44496119 (1997) Anthraquinone (99.2%) D462832; TXR 0052851 Acceptable/Guideline 1250, 2500, 5000 mg/kg	Negative. There were no induced increases in micronucleated bone marrow polychromatic erythrocytes (PCEs) relative to vehicle controls. The positive control induced significant increases in PCEs.
In vivo Mouse Bone Marrow Micronucleus Test	MRID 48370301 NTP Report (2005) D463729; TXR 0058228 Acceptable/Guideline 97-100% anthraquinone (AQ-OX) (Sample A70496/Lot No. 5893 used in 2 year bioassays) B6C3F1 male mice 500, 1000, 2000 mg/kg x 3 days via intraperitoneal injection	Negative up to the limit dose (2000 mg/kg). Anthraquinone did not induce a significant increase in micronuclei in bone marrow PCEs and is considered negative in the mouse bone marrow micronucleus test.
In vivo Mouse Peripheral Blood Micronucleus Test	MRID 48370301 NTP Report (2005) D463729; TXR 0058228 Acceptable/ Guideline 99.8% pure anthraquinone Male/female B6C3F1 mice 1875, 3750, 7500, 15000, 30000 ppm/dietary 14 weeks	Positive: There was a significant increase in the frequency of micronucleated normochromatic erythrocytes (NCEs) in female mice at 30,000 ppm only. Trend tests were positive for both sexes. An increased rate of erythropoiesis was observed in both sexes during the 14-week exposure at the highest dose, coinciding with a high percentage of polychromatic erythrocytes (PCEs), most notably occuring with a ~3-fold increase for females. Given that results were statistically significant only above the recommended limit dose, the positive results observed for this study are likely of low biological significance.
870.6200a Acute Neurotoxicity Screening Battery		Waived by HASPOC (M. Zampariello, TXR 0058067, 1/12/2021)
870.6200b Subchronic Neurotoxicity Screening Battery		Waived by HASPOC (M. Zampariello, TXR 0058067, 1/12/2021)

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile - 9,10-Anthraquinone		
Guideline No./ Study Type	**MRID No. (year)/TXR No. and/or DP Barcode/ Classification/Doses**	**Results**
870.7485 Metabolism and Pharmacokinetics (F344 Rat)	MRID 48370301 NTP report (2005) D462832; TXR 0052851 (included in chronic toxicity/carcinogenicity rat DER) Acceptable/non-guideline	F344/N rats were administered uniformly labeled ^{14}C-anthraquinone by intravenous (iv) injection of 0.35 mg/kg or by oral gavage at doses of 0.35 to 350 mg/kg. Results indicate that 9,10-anthraquinone was absorbed from the gastrointestinal tract and distributed to all tissues. The highest concentration of 9,10-anthraquinone was initially found in adipose tissue. However, by 96 hours less than 5% of the administered dose remained in major tissues, and no indication of bioaccumulation was apparent in any tissue. The majority of the radiolabeled 9,10-anthraquinone was eliminated in the feces and the urine by 24 hours after dosing for all concentrations. Elimination of >50% of the administered radioactivity in the feces suggested either substantial excretion of the parent and/or metabolites in the bile or poor GI absorption. Biliary excretion was confirmed by administering 9,10-anthraquinone to bile-duct cannulated rats. During the 6-hour period of sample collection, 35% of the administered dose was recovered in bile. Analysis of the bile samples showed that less than 3% of the radioactivity collected was present as the parent compound, suggesting extensive hepatic metabolism. Analysis of urine from dosed rats by high performance liquid chromatography revealed the presence of as many as 11 metabolites. Two of the metabolites identified were 1-hydroxyanthracene (or 1-hydroxyanthraquinone) and 2- hydroxyanthracene (or 2-hydroxyanthraquinone).
OPPTS 870.7800 28-Day Immunotoxicity (mouse)	MRID 48639804 (2011) TXR 0052851; D396314, D462832 Acceptable/Guideline 0, 500, 2000, or 7000 ppm (0, 98, 373, or 1245 mg/kg/day, respectively)	Systemic toxicity NOAEL =7000 ppm (1245 mg/kg/day); tested above the limit dose. LOAEL was not established Immunotoxicity NOAEL for anti-SRBC PFC response = 7000 ppm (1245 mg/kg/day); the LOAEL was not established (>7000 ppm).
Non-guideline Special Study Comparative Thyroid Assay		Waived by HASPOC (H. DeLeon, TXR 0058198, 7/29/2021)

A.3 Literature Search for Anthraquinone

Date and Time of Search: 03/04/2021; 11:38 am

Search Details:

((“*Anthraquinone”*)) AND (rat OR mouse OR dog OR rabbit OR monkey OR mammal)

PubMed* hits: 1610

Number of Swift** Articles: 982 for Animal
Number of Swift Articles: 1094 for Human
Number of Swift Articles: 0 for No Tag

The below details are from the 1st search performed in 2020

Date and Time of Search: 03/27/2020; 11:38 am

Search Details:

((“*Anthraquinone”*)) AND (rat OR mouse OR dog OR rabbit OR monkey OR mammal)

PubMed hits: 1482

Number of Swift Articles: 904 for Animal
Number of Swift Articles: 998 for Human
Number of Swift Articles: 0 for No Tag

All studies identified in the PubMed search were screened when the citation list was ≤100. Screening of larger citations lists (>100 citations) was conducted after prioritization in SWIFT-Review and focused on studies identified with the “Animal” and/or “Human” tag.

*PubMed is a freely available search engine that provides access to life science and biomedical references predominantly using the MEDLINE database.

**SWIFT-Review is a freely available software tool created by Sciome LLC that assists with literature prioritization. SWIFT-Review was used to prioritize citations lists that were larger than 100. Studies identified in the PubMed search were tagged and grouped based on the model of interest in the study (e.g. human, animal, *in vitro*, etc.).

Number of Articles Identified as Potentially Relevant for Risk Assessment: 4

Citations of Articles Identified as Relevant for Risk Assessment:

Dodd, DE; Layko, DK; Cantwell, KE; Willson, GA; Thomas, RS. "Subchronic toxicity evaluation of anthraquinone in Fischer 344." International Journal of Toxicology. Sept-Oct 2013;32(5):358-67.

Liberman, DF; Fink, RC; Schaefer, FL; Mulcahy, RJ; Stark, AA. Applied and environmental microbiology.1982. Mutagenicity of anthraquinone and hydroxylated anthraquinones in the Ames/Salmonella microsome system.

Hu, X; Wang, P; Hwang, HM. Bioresource technology. 2009. Oxidation of anthracene by immobilized laccase from Trametes versicolor.

Surh, I. et al. Toxicology and Carcinogenesis Study of Senna in the C3B6.129F1-*Trp*53^{tm1Brd} N12 Haploinsufficient Mice. Toxicol Pathol. 2013 July; 41(5): . https://doi.org/10.1177/0192623312464304

Conclusion of Literature Search: Following an in-depth screen, no studies were identified that contained relevant information (either quantitative or qualitative) that would impact the risk assessment or that would be considered in the selection of PODs for the anthraquinone human health risk assessment.

A.4 Executive Summaries

A.4.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity - Rat

MRID 48708301

In a 13-week dietary oral toxicity study (MRID 48708301), 9,10-anthraquinone (100% a.i.; Batch No. PEKXS20090409L01/1] was administered to four groups of 10 male and 10 female Sprague-Dawley rats/group at concentrations of 0, 500, 2000, or 7500 ppm (0, 40, 125, or 495 mg/kg/day in males; 0, 44, 150, or 661 mg/kg/day in females) for 4 consecutive weeks. Beginning with Week 5, due to effects on bodyweight and food consumption in all dosed groups, the 500 ppm diet was reduced to 200 ppm resulting in lowering the doses to 11 and 16 mg/kg/day for males and females, respectively, through the end of the 13-weeks. Neurological examinations were performed and included physical examination, arena observations, sensory reactivity, grip strength, and motor activity, as well as neurohistopathology.

One female rat at 661 mg/kg/day was sacrificed in extremis during Week 12 of the study. All other animals survived until scheduled sacrifice. A few females on the 661 mg/kg/day diet were thin with hunched posture toward the end of the treatment period. The majority of males and females at the high dose level had brown staining of the tail and dorsal body area. In females, mean body weights were decreased in a dose-dependent manner at 44/16 mg/kg/day (↓6-15%), 125 mg/kg/day (↓11-22%) and 661 mg/kg/day (↓13-31%) from weeks 1-13. The decreased body weights in females were considered adverse for all dose groups. In males, mean body weights were decreased at 125 mg/kg/day (↓8-14%) and 495 mg/kg/day (↓11-17%) from weeks 1-13. The decreased body weights in males at the mid- and high-dose were considered to be adverse since the decreases were >10%. Food consumption over the 13-week study period was low relative to controls for all treated groups. The greatest difference was observed at the mid- and high dose levels in which food consumption was 11-12% lower than controls in males and 21% lower in females at the mid dose and 13% lower at the high dose.

There was a statistically significant ($p \leq 0.01$ or $p \leq 0.05$) decrease in both forelimb and hindlimb grip strength in females at all dose levels. Hindlimb grip strength was lower in males at the mid- and high dose ($p \leq 0.05$). Although there were some statistically significant changes in forelimb and hindlimb strength, none were considered adverse. The motor activity was slightly reduced in females, and males were unaffected. The grip strength values were generally within the historical controls, and there was no observed histopathology identified related to neurotoxicity. Therefore, the neurobehavioral changes are not considered to be adverse.

Hematological changes (decreased hemoglobin, hematocrit, and erythrocyte counts and increased reticulocyte counts), increased spleen weights, and histopathological effects in the spleen were considered to be compensatory and not adverse due to a slight/minimal severity and apparent lack of progression.

Liver effects including increased liver weights and mineral/moderate hepatocellular hypertrophy that were observed in both sexes; however, in the absence of significant changes in liver

enzymes, these effects were considered to be adaptive and not adverse. Hepatocyte vacuolation (minimal to moderate) was seen at ≥125/150 mg/kg/day in males (4/10** mid, 4/10** high dose vs. 0/10 controls) and females (2/10 mid , 2/10 high dose vs 0/10 controls), and was considered to be adverse.

In females, statistically significant increases in kidney (relative to body) weights were seen at all dose levels (↑21%, ↑31%, ↑38%, low, mid, high-doses, respectively). Changes in clinical chemistry values (glucose↓[19%], cholesterol [↑141%], and triglycerides [↓47%]) were seen in high dose females. The incidence of basophilia of the cortical tubules in high dose females (4/10 vs 1/10 controls) was increased but not statistically significant, and was of minimal severity. At the mid- and high-dose groups, there was minimal to moderate pigment deposition in the cortical tubules (2/10 mid, 7/10* high vs 0/10 controls). In females, the suite of kidney effects (increased kidney weight, clinical chemistry changes in glucose, cholesterol and triglyceride, urinalysis changes (dark urine, presence of glucose and crystals in urine), and kidney histopathology (basophilia of the cortical tubules, pigment deposition in cortical tubules) seen at 661 mg/kg/day is considered to be adverse. Similar effects were seen in male rats (increased kidney weights, clinical chemistry changes, basophilia of the cortical tubules) in addition to cortical tubules with hyaline droplets at all dose levels. However, since α2μ-globulin does not explain all the kidney toxicity seen in males since similar effects were seen in female rats, it was determined that the kidney effects associated with α2μ-globulin cannot be distinguished from another mechanism that may be occurring. Therefore, the adversity decisions related to the kidney effects are made only for the females, and not the males, due to this uncertainty.

Thyroid follicular cell hypertrophy was observed in males at ≥125 mg/kg/day, with both the incidence and the severity of change being dose related. Increased thyroid weights were seen at 495 mg/kg/day in males. Thyroid hormone measurements were not taken. The thyroid effects (follicular cell hypertrophy and increased thyroid weight) in males were considered to be adverse. Increased thyroid weights were seen in females; however, due to the lack of a dose response and in the absence of corroborating histopathology, the thyroid findings in females were not considered to be adverse.

Statistically decreased absolute and relative (to brain) adrenal weights were seen across all dose groups in females (↓17/↓15 low ↓22/↓20 mid, ↓25/↓21 high dose). Minimal to moderate hypertrophy/hyperplasia of the adrenal gland zona glomerulosa was observed in the majority of females at the mid (7/10**) and high (9/10**) dose groups vs 0/10 in controls. The decreased adrenal weights and histopathology at ≥150 mg/kg/day were considered to be adverse. Adverse changes in the reproductive tract of females at the high dose included minimal to moderate interstitial cell hyperplasia (6/10** treated vs 0/10 controls) of the ovaries, which was accompanied by the presence of atrophy/mucification of the vagina (4*/10 vs 0/10 controls) and moderate myometrial atrophy of uterus (3/10 vs 0/10 controls). Ovarian weights (both absolute and relative to brain weight) were statistically decreased at the mid- (↓27%, ↓24%, respectively) and high- (↓35%, ↓32%, respectively) doses. Decreased uterus/cervix weights were seen at the high dose (↓44% absolute, ↓41% relative to brain weight). In the females at the high dose, there was also multifocal foreign body giant cell reaction, associated with crystals in the liver, kidneys, urinary bladder (associated with urinary bladder hyperplasia), lungs, heart, skeletal muscle, diaphragm, skin (dermis; associated with epidermal hyperplasia), gastro-intestinal tract

(predominantly in the ileum and rectum), nervous system (brain, spinal cord and, on one animal, optic nerve), lymph nodes (associated with sinus histiocytosis in the mesenteric lymph nodes) and uterus. The presence of foreign body giant cell reaction associated with crystals in various sites suggests presence of precipitate of the test material and/or its metabolite(s), and its deposition in various sites leading to a reaction by the body to contain the spread of this material.

The LOAEL = 44 mg/kg/day, based on decreased body weight in females. The NOAEL was not observed. [Note: After the low dose was decreased from 40 to 11 mg/kg/day in males and from 44 to 16 mg/kg/day in females beginning on week 5, the body weight decreases remained flat (i.e., no trend related increase over time (week 7 [↓8% males, ↓15% females] and week 13 [↓6% males, ↓13% females]). In females, the decreased body weight at weeks 7 and 13 of >10% was considered to be a carryover effect from the higher dose of 44 mg/kg/day rather than 16 mg/kg/day; therefore, the LOAEL was set at 44 mg/kg/day (the lowest dose originally tested), instead of 16 mg/kg/day. At the higher doses, the body weight decreases became greater over time. This effect was more pronounced in females.]

This dietary 13-week toxicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement for a 13-week toxicity study in rodents (OCSPP 870.3100).

MRID 48370301

In a subchronic oral toxicity NTP study (MRID 48370301), groups of ten F344/N rats/sex/dose were administered anthraquinone (99.8% a.i.; Lot # 5893) via the diet at nominal dose levels of 0, 1875, 3750, 7500, 15000, or 30,000 ppm (equivalent to 0, 135, 275, 555, 1130, and 2350 mg/kg/day in males and females) for up to 14 weeks. During the study, clinical condition, detailed physical examination, bodyweight, food consumption, hematology, blood chemistry, urinalysis, organ weight, macropathology, and histopathology investigations were undertaken. Reproductive tissues were evaluated, including sperm motility and vaginal cytology.

There were no effects of treatment on mortality, clinical signs of toxicity, body weight in males, food consumption, or spermatozoal measurements.

For most effects seen, the dose response data in the NTP study showed a point at which all animals were affected and with similar severity. Generally, as the dose increased, there was no corresponding increase in incidence or severity. Toxicokinetic data from the chronic NTP rat study illustrated kinetics potentially responsible for this non-linear response. The data showed that after oral exposure, anthraquinone is slowly and incompletely absorbed, slowly distributed to tissues by a diffusion-limited transport process, stored in fatty tissues, and slowly metabolized via a saturable kinetic process.

Hematological changes (decreased hemoglobin, hematocrit and erythrocyte counts and increased reticulocyte count) and histopathological effects in the bone marrow and spleen were mild and were considered to be compensatory and not adverse due to a slight/minimal severity and lack of progression.

In females, treatment-related increases in urinary N-acetyl-β-D-glucosaminidase (NAG) enzyme activity at Week 13 (↑40-173%) occurred at all dose levels; however, the NAG enzyme activity

increase of 107% (or a doubling from controls) in females only at ≥275 mg/kg/day was considered to be adverse. Increases in NAG activity occur prior to hyaline droplet accumulation and nephropathy and act as a protective mechanism[23]. Additionally, increases in NAG act as an early indication of tubular dysfunction resulting from renal disease and nephrotoxic damage. Absolute and relative (to body weight) right kidney weights were statistically increased in females (↑12-20% and 17-41%, respectively) across all dose groups (≥135 mg/kg/day). The incidence of kidney nephropathy was increased in females at ≥555 mg/kg/day (5/10, 8/10 and 10/10, respectively, vs. 3/10 controls), with severity increasing slightly from minimal to mild. All females in all treated groups displayed kidney hyaline droplet accumulation (10/10 (SS) treated vs 0/10 controls). The kidney nephropathy and hyaline droplet accumulation in females was considered adverse at ≥555 mg/kg/day. Male rats also had similar kidney histopathology (nephropathy and hyaline droplet accumulation) seen at all dose levels (including controls for nephropathy). However, since these effects were also seen in females, it was determined that the kidney effects that result from the $\alpha_{2\mu}$-globulin, which was measured in males, cannot be distinguished from another mechanism that may be occurring in males. Therefore, the adversity decisions on the kidney effects are being made only for the females and not the males due to this uncertainty.

Absolute and relative liver weights were statistically increased in the males (↑25-66% and 21-75%, respectively) and females (↑39-102% and 43-137%, respectively) across all dose groups. No changes in liver enzymes were seen. All males and females in all treated groups displayed liver hypertrophy (10/10 (SS) treated vs 0/10 controls). The lack of liver enzyme increases supports the decision of not considering the hypertrophy or changes in liver weights to be adverse.

At ≥275 mg/kg/day, all males and females displayed minimal thyroid follicular cell hypertrophy (10/10 all doses vs. 0/10 control). The top 2 doses in this study were greater than the limit dose. The lack of severity progression suggests this is not a very sensitive endpoint. The dose response is consistent with the ADME data as discussed above. The thyroid effects are considered to be adverse, especially given that thyroid weights and thyroid hormones were not measured.

At ≥555 mg/kg/day, final mean body weights in females were statistically decreased by 12-16%, and overall (Weeks 1-14) body weight gains were decreased by 25-34%. Since the decreased body weight was >10%, it was considered to be adverse.

At ≥1130 mg/kg/day, there were dose-dependent increases in estrous cycle length (5.40 and 6.15 days, respectively) compared to the controls (4.55 days).

At 2350 mg/kg/day in females, urinary bladder inflammation (6/10** high dose vs 0/10 controls) was seen with minimal to mild severity. Minimal to mild transitional epithelium hyperplasia (9/10 treated vs. 0/10 controls) in the urinary bladder was also seen in the high dose females.

[23] Price RG. The role of NAG (N-acetyl-beta-D-glucosaminidase) in the diagnosis of kidney disease including the monitoring of nephrotoxicity. Clin Nephrol. 1992;38 Suppl 1:S14-9.]

The LOAEL = 275 mg/kg/day based on increased urinary *N*-acetyl-β-D-glucosaminidase (NAG) enzyme activity in females and thyroid follicular cell hypertrophy in both sexes. The NOAEL = 135 mg/kg/day. The increased NAG enzyme activity is considered to be a precursor of kidney damage and a very sensitive and reliable metric for kidney disease.

This study is classified as **Acceptable/Non-guideline**.

870.3100 90-Day Oral Toxicity – Mouse

MRID 48370301

In a subchronic oral toxicity NTP study (MRID 48370301), groups of ten $B6C3F_1$ mice/sex/dose were administered 9,10-anthraquinone (99.8% a.i.; Lot # 5893) via the diet at nominal dose levels of 0, 1875, 3750, 7500, 15,000, or 30,000 ppm (equivalent to 250/300, 500/640, 1050/1260, 2150/2600, and 4300/5300 mg/kg/day in males/females, respectively) for up to 14 weeks.

There were no effects of treatment on mortality, clinical signs of toxicity, body weights or body weight gains, food consumption, spermatozoal measurements, or estrous cycle lengths.

At ≥1875 ppm (300 mg/kg/day)**,** hematocrit, hemoglobin, and erythrocyte count were significantly decreased in females (↓3-8%, ↓2-5%, and ↓5-12%, for hematocrit, hemoglobin and erythrocytes, respectively) at Week 14. There was no decrease noted in males until the high dose. Hematocrit, hemoglobin, and erythrocyte count were statistically decreased in high dose males (↓11%, ↓6%, and ↓13%, respectively) at Week 14. Also at Week 14, there were increases in reticulocytes in males (↑33-67%) and females (↑60-160%), mean corpuscular volume (MCV) in females (↑2-4%), mean corpuscular hemoglobin (MCH) in females (↑3-7%), and mean corpuscular hemoglobin concentration (MCHC) in females (↑2-4%). In the spleen, there were increased ($p<0.01$) incidences, but not severity (minimal), of hematopoietic cell proliferation in ≥1875 ppm (≥250/300 mg/kg/day) males (6/10, 10/10, 10/10, 10/10, and 9/10, respectively, vs. 0/10 control) and females which showed minimal to mild severity with increased dose (9/10 [NS], 10/10, 10/10, 9/10 [NS], and 9/10 [NS], respectively, vs. 6/10 control). Also in the spleen, pigmentation was observed in ≥1875 ppm males (≥250 mg/kg/day) (10/10, 10/10, 10/10, 10/10, and 9/10, respectively, vs. 0/10 control) with all severity of minimal/mild. Pigmentation of the spleen was observed in all female groups including controls (10/10, 10/10, 10/10, 9/10, and 9/10, respectively, vs 10/10 control) with mild severity in all treated groups. The hematology changes (decreased hemoglobin, hematocrit and erythrocyte counts) along with the histopathological effects in the spleen were considered to be compensatory and not adverse due to the slight/minimal severity and the apparent lack of progression.

There were increased ($p<0.01$) incidences of cytoplasmic alteration of the transitional epithelial cells of the urinary bladder in all animals at ≥1875 ppm (males: 10/10 all treated vs. 0/10 control and females:10/10 at each dose vs. 0/10 control), with increasing severity (minimal to marked) with dose. The urinary bladder effect was considered adverse in males at ≥3750 ppm(≥500 mg/kg/day) and in females at ≥15,000 ppm (≥2600 mg/kg/day) when severity increased to moderate or greater.

Absolute and relative (to body) liver weights were statistically increased ($p \leq 0.01$) in ≥1875 ppm (≥250/300 mg/kg/day) males (↑15, ↑22, ↑37, ↑49, ↑76% absolute and ↑12, ↑19, ↑33, ↑55, ↑80% relative, respectively) and females (↑20, ↑29, ↑36, ↑58, ↑89% absolute and ↑11, ↑23, ↑28, ↑51, ↑87%, respectively). There was an increased ($p<0.05$) incidence of centrilobular hypertrophy in the liver at ≥3750 ppm (≥500 mg/kg/day) in males (9/10, 10/10, 10/10, and 10/10, respectively, vs. 0/10 control) and at ≥3750 ppm (640 mg/kg/day) in females (5/10, 9/10, 7/10, and 10/10, respectively, vs. 0/10 control). The increased liver weights were supported by liver histopathology at ≥3750 ppm (500/640 mg/kg/day) and were considered to be adverse.

The LOAEL = 500/640 mg/kg/day, male/female based on increased liver weights (both sexes) and microscopic findings in the liver (centrilobular hypertrophy) in both sexes and urinary bladder (cytoplasmic alteration of the transitional epithelium) in males. The NOAEL = 250/300 mg/kg/day, males/female.

This study is classified **acceptable/non-guideline**.

870.3150 90-Day Oral Toxicity - Dog

Waived by HASPOC (K. Yozzo, TXR 0057823, 1/29/2019)

870.3200 21/28-Day Dermal Toxicity – Rat

MRID 48639801

In a 28-day dermal toxicity study (MRID 48639801), Anthraquinone (100% a.i., batch/lot # PEKXS20090409L01/1) was applied to the shaved skin of 10 Sprague-Dawley (Crl:CD (SD)) rats/sex/dose at dose levels of 0, 100, 300, or 1000 mg/kg bw/day, 6 hours/day for 5 days/week for 3 weeks and 7 days/week for the fourth week over a 28-day period.

There were no compound related effects on mortality, clinical signs, body weight, or food consumption at any dose level.

The hepatocyte hypertrophy seen in the liver at 1000 mg/kg/day was not accompanied by any changes in liver weights or clinical chemistry parameters that would normally indicate a toxic response. This was considered to be an adaptive effect and not adverse. Increased focal hepatocyte necrosis was seen at 1000 mg/kg/day in males (4/10 males [2 minimal, 2 moderate] vs 2/10 controls [1 minimal, 1 slight]) and females (2/10 minimal severity vs 0/10 controls). The liver necrosis was considered to be adverse. In addition, follicular cell hypertrophy in the thyroid of minimal severity was seen in high dose males (0/10, 1/10, 1/10, and 6/10 for 0, 100, 300, and 1000 mg/kg/day). Thyroid hormones were not measured. The thyroid follicular cell hypertrophy in males was considered to be an adverse effect.

Kidney effects, including increased kidney weights and cortical tubule with hyaline droplets, were seen in males. Since the kidney effects are solely based on males with no kidney effects seen in females, it was assumed that the kidney effects in males were related to the suite of α2μ-globulin effects and were not considered to be adverse or relevant to humans.

The mild hematology changes (decreased hemoglobin, hematocrit and erythrocyte counts) and the histopathological effects on the spleen seen at the high dose were considered to be compensatory and not adverse.

No effects were seen at 100 or 300 mg/kg/day.

No persistent dermal changes were seen.

The LOAEL is 1000 mg/kg/day (highest dose tested) based on thyroid follicular cell hypertrophy in males and focal hepatocyte necrosis. The NOAEL is 300 mg/kg/day.

This 28-day dermal toxicity study in the rat is acceptable (guideline) and satisfies the guideline requirement for a 28-day dermal toxicity study (OCSPP 870.3200; OECD 410) in rats.

870.3465 90-Day Inhalation – Rat

Waived by HASPOC (K. Yozzo, TXR 0057823, 1/29/2019)

A.4.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat

In a developmental toxicity study (MRID 48639803), anthraquinone (100% a.i.; batch No. PEKXS20090409L01/1) was administered to 22 mated female Crl:CD(SD) rats/dose by gavage in corn oil at dose levels of 0, 10, 50, or 150 mg/kg bw/day on gestation days (GDs) 6 through 19. Surviving dams were sacrificed and necropsied on GD 20. All fetuses were weighed, sexed, and examined externally; approximately one-half were subjected to skeletal evaluation, and the remaining one-half were subjected to visceral examination by a free-hand serial sectioning technique. Placentae were also weighed individually and examined grossly. Dose selection was based on a preliminary developmental toxicity study (MRID 48639802).

There were two mortalities, neither of which could be definitively attributed to treatment. There were no dose-dependent clinical signs. All treated groups had mean body weight loss during GD 6-7 (-3, -4, and -5 grams (g) at the low, mid and high dose, respectively), compared to a 2 g weight gain for controls. Low- and mid-dose dams resumed weight gain after GDs 7-8. Maternal body weights were significantly decreased at the high dose (8-11%) compared to controls after GD 9. When adjusted for gravid uterine weight, high-dose dams showed a 12% decrease. Corresponding effects on food consumption were seen. Low-dose females had decreased food consumption from GD 6-9 (↓14%; $p<0.01$), mid-dose females had decreased food consumption from GD 6-9 and 10-13 (↓27% and ↓ 9%, respectively; $p<0.01$), and high-dose females had decreased food consumption during GD 6-9, 10-13, and 18-19 (↓46%, ↓22%, and ↓22%, respectively; $p<0.01$). **The maternal LOAEL is 150 mg/kg/day, based on decreased body weight and food consumption. The maternal NOAEL is 50 mg/kg/day.**

The mean numbers of corpora lutea, implantations, viable fetuses, early and late resorptions, pre- and post-implantation losses, and fetal sex ratios of the treated dams were similar to those of

controls. At the highest dose level mean fetal weight was decreased in both sexes and combined, (↓12%, ↓8%, ↓10% for males, females, and combined, respectively; p<0.01). Mean litter weight was decreased (↓12%, p<0.01), and mean placental weight also was decreased (↓11%, p<0.05) at the highest dose level. Maternal treatment did not increase the incidences of major abnormalities, minor abnormalities, or developmental variants. **The developmental LOAEL is 150 mg/kg/day, based on decreased fetal weight (both sexes), litter weight, and placental weight. The developmental NOAEL is 50 mg/kg/day.**

This developmental toxicity study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OCSPP 870.3700; OECD 414) in the rat.

870.3700b Prenatal Developmental Toxicity Study – Rabbit

In a developmental toxicity study (MRID 50131501), anthraquinone (97.2% a.i., lot H121226) was administered to 20 pregnant New Zealand White [Hra:(NZW)SPF] rabbits/dose by gavage at dose levels of 0, 25, 50, or 100 mg/kg bw/day from days 6 through 28 of gestation (GD 6-28).

There was a significant dose-dependent increase in unscheduled deaths (0% control, 5% low, 20% mid and 45% high dose). At the high dose, most premature deaths were associated with late abortions (gestation days (GDs) 24-26). There were also two abortions (not associated with death) in the mid dose group that occurred late on GD 25 and 28. Two does at the mid dose and two at the high dose were found dead. Two does were euthanized (one low dose and one high dose). All premature deaths (regardless of abortion) were associated with weight loss, decrease food intake and clinical signs. Body weight changes for early decedents occurred at all dose levels (↓17% low; ↓3-15% mid, ↓9-27% high dose). Mean daily food intake was also significantly decreased for the early decedents (7-104 g/day compared to 142 g/day controls). Most early decedents had normal necropsies, except one mid dose doe. The following clinical signs were observed in most of the early decedents (especially at the mid and high doses): decreased feces, thin appearance, ungroomed fur, suspected dehydration, and red urine. Furthermore, there was a general, dose-dependent increase in the same clinical signs for does that survived to the end of the study.

For all animals combined (unscheduled deaths and survivors to end of study), decreased feces and red urine were significantly increased at the mid and high doses, while other clinical signs were significantly increased only at the high dose. Body weight was significantly decreased (compared to controls) in a dose-dependent manner. Absolute body weight decreases were significant at 100 mg/kg/day (↓6-15% compared to controls) starting on GD 9 and through the rest of the assay. Similarly, body weight was significantly decreased at the 50 mg/kg/day (↓4-8%) starting on GD 15. Mean overall body weight gain (GD 6-29) was significantly decreased at all treatment doses, even after correcting for uterine weight. A reduction of 10% or more in body weight was considered an adverse l effect, therefore, the decreased body weight at 100 mg/kg/day, and not 50 mg/kg/day, was considered to be adverse. Necropsy observations were few and did not occur in a dose-dependent manner. **The maternal LOAEL is 50 mg/kg bw/day, based on increased mortality (20%), late abortions (gestation days 25 and 28), and clinical signs (decreased feces output and red urine). The maternal NOAEL is 25 mg/kg bw/day.**

As described previously, abortions were observed in 2 mid dose does and 6 high dose does, but not in the control or low dose does. Although not statistically significant, there was an increase in the number of late resorptions and percent post-implantation loss in the high dose group in comparison with the control group values, which were outside of the corresponding historical control ranges. Average fetal body weights were statistically significantly reduced ($p \leq 0.01$) in the high dose group in comparison with the control group values (↓20% combined, ↓20% male and ↓17% female) and are considered to be adverse. While mean fetal weights were also decreased at >5% in the low and mid-dose groups, the decreased fetal weights are not considered to be adverse since the decreases were not statistically significant, are within the variability of the concurrent controls, are very close to the low end of the historical control range, do not follow a dose response, and have high variability. There were very few external and visceral findings in the fetuses, and they did not occur in a dose-dependent manner. A few skeletal variations occurred in all treated groups but not in controls: pubis, incomplete ossification; pubis, unossified; skull, hyoid ala, bent; and sternebra, fused. Of these observations, only variations of the pubis seem to occur in a dose-dependent manner. All incidences were within historical control ranges, except unossified pubis and net hyoid ala, which did not occur in the historical controls. Overall, the reviewer did not consider any of these skeletal variations as treatment related because they occurred at very low incidences, were not statistically significant, and/or were within the historical control ranges. **The developmental LOAEL is 50 mg/kg/day based on late abortions. The developmental NOAEL is 25 mg/kg/day.**

This developmental toxicity study in the rabbit is classified **acceptable (guideline)** and **satisfies** the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in rabbit.

A.4.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects - Rat

Waived by HASPOC (M. Zampariello, TXR 0058067, 1/12/2021)

A.4.4 Chronic Toxicity

870.4200 Carcinogenicity – Mouse

MRID 48370301

In an NTP carcinogenicity study (MRID 48370301), groups of 50 $B6C3F_1$ mice/sex/dose were administered 9,10-anthraquinone (99.5-99.9% a.i.; Lot # 5893) in the diet at dose levels of 0, 833, 2500, or 7500 ppm (equivalent to 0/0, 90/80, 265/235, or 825/745 mg/kg/day in males/females) for up to 105 weeks.

There were no effects of treatment on clinical signs or food consumption.

At ≥90/80 mg/kg/day, hepatocellular centrilobular hypertrophy was statistically increased in all exposed groups of males (24/50 [1.3] controls, 34/50* [1.5], 41/50** [1.8], 33/50* [2.5]) and females (1/49 [1.0] controls, 27/50** [1.2], 22/50** [1.2], 39/49** [1.5)]. Severity progressed

from minimal to moderate in males and from minimal to mild in females and was considered to be adverse. Liver weights and clinical chemistry were not measured in this study. In the absence of these data the liver hypertrophy was conservatively considered to be adverse. In addition, the liver hypertrophy was considered to be supportive of the liver tumors seen in both sexes. In high dose females, there was an increase in fatty focal degeneration (9/49* [1.2] high dose vs 2/49 [1.5] in controls) and in eosinophilic focus (22/49** vs 0/49 controls). In males, at the high dose there was a statistical increase in hematopoietic cell proliferation (4/49* [1.0] vs 0/50 controls) and focal necrosis (8/49* [2.1] vs 2/50 [1.5] controls). The liver effects were considered to be adverse. Treatment-related liver tumors were seen in male and female mice.

The incidences of thyroid follicular cell hyperplasia (minimal to mild) in 265 mg/kg/day (mid dose) and 825 mg/kg/day (high dose) males were significantly greater than those in the controls (7/50 [1.3 severity] control, 10/50 [1.4] low, 15/49* [1.1] mid, and 21/46** [1.2] high dose). The incidences of thyroid follicular cell hyperplasia (minimal to mild severity) were increased in exposed groups of females, but the differences from controls were not statistically significant (10/45 [1.7] control, 14/50 [1.2] low, 16/49 [1.2] mid and 15/48 [1.5] high dose). Even though the findings in females were not statistically significant, they are consistent with the thyroid effects seen throughout the database. Thyroid hormones were not measured. Therefore, the thyroid effects at ≥265/235 mg/kg/day in both sexes were considered to be adverse. In addition, thyroid follicular cell tumors were seen in both sexes at 825/745 mg/kg/day, M/F).

At 825 mg/kg/day, body weights were decreased in males beginning at Week 82 and continuing throughout the end of the study (↓5-21%) but there were no significant changes in body weights in females throughout the study.

The LOAEL = 90/80 mg/kg/day based on microscopic findings in the liver (centrilobular hypertrophy). A NOAEL was not established.

Carcinogenicity (from CARC report (J. Rowland and K. Middleton, TXR 0056478, *10/21/2012*)
Liver: Male mice showed significant (trend and pair-wise) increases in the incidences of adenomas, carcinomas, hepatoblastomas, and the combined tumors at 833, 2500 and 7500 ppm (except for carcinomas at 833 ppm). Female mice showed significant (trend and pair-wise) increases for adenomas and the combined tumors at all doses (833, 2500 and 7500 ppm). Significant increases in carcinomas were seen only at 2500 and 7500 ppm. There were no significant increases in hepatoblastomas at any level. The tumors were corroborated with significant increases in centrilobular hypertrophy at all dose levels in both sexes. **Therefore, the CARC determined that the liver tumors in both sexes of mice are treatment-related.**

Thyroid gland: Male mice showed a significant (trend and pair-wise) increase in thyroid follicular cell adenomas at 7500 ppm when compared to controls. The incidence rate was outside of the historical control range. Female mice showed only a significant trend for thyroid follicular cell tumors. Although not statistically significant (pair-wise comparison), there is concern for the thyroid tumors in females since there is a malignant component (increased incidence of carcinomas compared to control) and the incidences are outside of the historical control range. Additionally the thyroid tumors occurred in conjunction with a significant increase in follicular cell hyperplasia and compliments the tumors observed in males. **Therefore, the CARC**

determined that the thyroid tumors in male and female mice are treatment related.

This study is classified **acceptable/non-guideline**.

870.4300 Combined Chronic Toxicity/Carcinogenicity – Rat

MRID 48370301

In an NTP carcinogenicity study (MRID 48370301*)*, groups of 50-60 F344/N rats/sex/dose (60/sex in the control and high-dose groups and 50/sex in all remaining treatment groups) were administered anthraquinone (99.83-99.85% a.i.; Lot # 5893) in the diet at dose levels of 0, 469, 938, 1875, or 3750 ppm (equivalent to 0/0, 20/25, 45/50, 90/100, and 180/200 mg/kg/day in males/females) for up to 105 weeks. Interim evaluations were conducted on five rats/sex in the 0 and 3750 ppm groups at 3 months (microscopic pathology and soluble protein content and α_{2u}-globulin concentration in right kidney samples) and 12 months (microscopic pathology and selected organ weights [left and right kidney and liver]). Plasma concentrations of anthraquinone were determined for a subset of rats on day 8 (18 males/dose) and at 3, 6, 12, and 18 months (10 rats/sex/dose) for toxicokinetic analysis to determine C_{min}/C_{max} and T_{min}/T_{max} estimates, and after a single gavage dose of 100 mg/kg in 0.2% methylcellulose and 0.1% Tween 80 in previously undosed rats (2-3/sex) at five time points to extrapolate plasma dosimetry from single-dose studies to chronic exposure. Also, as part of the current study, the metabolism and disposition of anthraquinone in male rats was examined after intravenous injection of labeled ^{14}C-anthraquinone at 0.35 mg/kg or by gavage at doses ranging from 0.35 to 350 mg/kg.

There were no adverse effects of treatment on mortality, clinical signs, and food consumption.

Toxicokinetics analyses showed that plasma C_{max} estimates were approximately 2- to 3-fold greater in female rats compared to males for each collection period, suggesting an overall increased exposure to anthraquinone in females administered the test compound in the diet. After oral exposure, anthraquinone is slowly and incompletely absorbed directly into venous blood, slowly distributed to tissues by a diffusion-limited transport process, and is slowly metabolized via a saturable kinetic process. This likely contributes to the non-linear response of nearly all measured parameters, seen as a lack of a corresponding increase in incidence or severity with increasing dose. Tissue concentrations in female rats are higher due to slow clearance and slower metabolism. Anthraquinone accumulates in tissues due to faster absorption compared to elimination, especially in females. Feces is the predominant route of elimination, with little parent remaining after extensive hepatic metabolism and enterohepatic cycling.

Body weight decreases of ≥10% were seen in all treated females at ≥25 mg/kg/day and were considered to be adverse. There was a dose-time relationship observed, as these decreases were seen beginning at Week 38, at Week 26, at Week 22, and at Week 14 in the 25, 50, 100, and 200 mg/kg/day treatments, and generally occurred in a dose-dependent manner. There was no effect of treatment on body weight of males, as decreases were noted sporadically and remained at 5-7% relative to the control.

Alpha$_{2\mu}$-globulin was quantified in the kidney at the 3-month interim, and results showed that the concentrations of $\alpha_{2\mu}$-globulin in the kidney of high-dose males were greater than that in the

control group, while in high-dose females they were lower than in the control group. At the 12-month interim evaluation in female rats at the high dose, absolute kidney weight was significantly increased by 6% in the right kidney, with no change relative to control in the left kidney. Relative kidney weights were significantly increased by 38-40% in the right and left kidneys. The incidences of mild to moderate kidney hyaline droplet accumulation were increased at both the 3-month and 12-month interim evaluations in the high-dose female rats. Minimal to mild nephropathy also was noted in some high dose females (2/5 treated vs. 1/5 control) at 3-months and most females at 12-months (5/5 treated vs. 3/5 control). Minimal mineralization of the renal medulla was increased in high-dose male rats (5/5 treated vs. 0/5 control) and in high-dose female rats (4/5 treated vs. 1/5 control) at the 12-month interim evaluation.

At the two-year evaluation, statistically increased incidences of minimal to mild hyaline droplet accumulation in the kidneys were noted at all dose levels for females. Nephropathy was significantly increased in females at all doses relative to the control (47-49/50 treated vs. 39/50 control) with similar severity (minimal to mild) noted across all dose groups. Incidences of minimal to mild pigmentation of the kidney were significantly increased in all treated females (47-50/50 treated vs. 27/50 control). Similar effects were seen in male rats (accumulation of hyaline droplets, nephropathy, pigmentation) at all dose levels. Incidences of mineralization of the renal medulla were significantly increased in all treated males (42-49/50 treated vs. 30/50 control) with a slight increase in severity at ≥90 mg/kg/day, while significant but minor increases were seen in the 50 and 100 mg/kg/day females (27-28/50 treated vs. 17/50 control) with no increase in severity. No significant effects on renal tubule hyperplasia were observed in treated males, but significantly increased incidences of renal tubule hyperplasia (minimal to mild severity) were noted in all treated females (11-15/50 treated vs. 0/50 control). Although $\alpha_{2\mu}$-globulin staining was measured in both sexes in the NTP study, $\alpha_{2\mu}$-globulin does not explain all kidney toxicity seen in male rats since similar effects were also seen in female rats. Therefore, it was determined that the etiology of the kidney toxicity in males cannot be attributed solely to $\alpha_{2\mu}$-globulin; another mechanism may also be occurring. The adversity decisions related to the kidney effects are made only for the females, and not the males, due to this uncertainty. Therefore, in females at ≥25 mg/kg/day, the kidney effects, including hyaline droplet accumulation, nephropathy, pigmentation, renal tubular hyperplasia, and mineralization of medulla were considered to be adverse. The kidney mineralization seen at all doses in males was also considered to be adverse since this effect is not a typical effect that is seen with the $\alpha_{2\mu}$-globulin suite of effects.. The urinary bladder transitional epithelial hyperplasia seen at ≥100 mg/kg/day in females was also considered to be adverse.

Increased liver weights and centrilobular hypertrophy were observed in both sexes at the 3-month, 12-month and 2 year evaluations and were considered to be adaptive. Significantly increased incidences in microscopic liver findings of minimal to mild severity were seen at the two-year evaluation in both sexes at all dietary concentrations and included cystic degeneration, inflammation, and eosinophilic and mixed-cell foci, and cytoplasmic vacuolization in males. These liver effects were considered to be adverse.

Histopathological effects in the bone marrow and spleen were considered to be compensatory and not adverse due to the slight/minimal severity, consistent with other studies in the database.

The LOAEL = 20/25 mg/kg/day, M/F, based on decreased body weight in females, kidney histopathological effects, including hyaline droplet accumulation, nephropathy, pigmentation, renal tubular hyperplasia, and mineralization of medulla in females and mineralization of medulla in males, as well as several liver histopathological effects, including cystic degeneration, inflammation, and eosinophilic and mixed-cell foci in both sexes, and cytoplasmic vacuolization in males. The NOAEL was not established.

Carcinogenicity (from CARC report (J. Rowland and K. Middleton, TXR 0056478, 10/21/2012)

Urinary Bladder Transitional Epithelial and Kidney Tumors: Male F344 rats had a significant increase (pairwise comparison) in urinary bladder transitional epithelial papillomas only at 1875 ppm. There was no dose-response or corroborative non-neoplastic lesions in the urinary bladder. Male rats also showed an isolated increase in renal tubule adenomas only at the 938 ppm dose in the absence of dose-response, progression to malignancy (i.e., no carcinomas), and corroborative non-neoplastic lesions. Furthermore, the precursor events associated with α2μ-globulin accumulation (CIGA) were in place for the male rats but did not lead to renal tubule neoplasms. Consequently, the response observed in the male rat is not indicative of a male rat-specific CIGA tumor induction. **The CARC determined that urinary bladder and kidney tumors observed in male rats were not treatment-related.**

Kidney Tumors: In the female rats, when compared to controls, there were significant (trend and pair-wise) increases in renal tubule adenomas and combined adenomas/carcinomas in the 938, 1875 and 3750 ppm dose groups. Additionally, there was an increase (trend and pair-wise) in the incidences of combined adenomas/carcinomas at the low dose (469 ppm). The combined tumor incidences were outside the historical control range. There were no increases in carcinomas at any dose level. The presence of increased renal tubule hyperplasia and nephropathy in the absence of α2μ-globulin suggests that the tumors observed were treatment related but not linked to CIGA. For the females, the CIGA mode of action (MOA) of kidney tumor induction was ruled out since female rats are not known to accumulate low-molecular weight proteins. **Therefore, CARC determined that the kidney tumors in female rats are treatment-related.**
Thyroid Tumors: In female rats, when compared to controls, there were only significant trends (not pair-wise) for thyroid gland c-cell adenomas, carcinomas, and/or adenomas/carcinomas combined. However, there were no corroborative non-neoplastic lesions (e.g., hyperplasia) and the incidences were within the historical control range. **Therefore, the CARC determined that the thyroid tumor response in female rats was not treatment-related.**

This study is classified **acceptable/non-guideline**.

A.4.5 Neurotoxicity

870.6200 Acute Neurotoxicity Screening Battery

Waived by HASPOC (M. Zampariello, TXR 0058067, 1/12/2021)

870.6200 Subchronic Neurotoxicity Screening Battery

Waived by HASPOC (M. Zampariello, TXR 0058067, 1/12/2021)

A.4.8 Metabolism

870.7485 Metabolism - Rat

See 870.4300 for metabolism summary

870.7600 Dermal Absorption - Rat

Not required

A.4.9 Immunotoxicity

870.7800 Immunotoxicity

MRID 48639804

In a dietary immunotoxicity study (MRID 48639804), anthraquinone (100% a.i., Batch No. PEKXS20090409L01/1) was administered to female Crl:CD1(ICR) mice (10/group) at concentrations of 0, 500, 2000, or 7000 ppm (0, 98, 373, or 1245 mg/kg/day, respectively) for 4 consecutive weeks. A positive control group of 8 female mice received basal diet throughout the study and received daily oral (gavage) doses of cyclophosphamide at 20 mg/kg/day on days 22-26. On Day 25, all animals were given with sheep red blood cells (SRBC; $4x10^8$ cells/animal) by intravenous injection. Four days after injection (day 29), animals were killed by carbon dioxide asphyxiation followed by exsanguinations. The spleen was removed from each mouse and splenocyte suspensions were prepared. Anti-SRBC antibody responses were measured with a plaque forming cell (PFC) assay.

There were no significant treatment-related effects seen on clinical signs, mortality, body weights, body weight gains, food consumption, or organ (thymus, spleen, and brain) weights.

The systemic toxicity NOAEL is 7000 ppm (1245 mg/kg/day); tested above the limit dose.

There are no statistically significant changes in the antibody response in any of the three treated groups with the PFC assay, in the numbers of cells/spleen, specific activity (PFC/10^6 cells), or total activity (PFC/spleen), when compared to the control. High inter-individual variability was noted in all the treatment groups as well as in the control group. Evaluation of individual animal data of this study did not show any trend or distribution that would demonstrate significant suppression of anti-SRBC PFC response. The positive control with cyclophosphamide resulted in a marked and statistically significant reduction of the anti-SRBC PFC response compared to the control and validated the sensitivity of the assay.

The Natural Killer (NK) cells activity was not evaluated in this study. The toxicology database for anthraquinone does not reveal any evidence of treatment-related effects on the immune

system. The overall WOE suggests that this chemical does not directly target the immune system. Under HED guidance, a NK cells activity assay is not required at this time.

Under conditions of this study, the immunotoxicity NOAEL for anti-SRBC PFC response is 7000 ppm (1245 mg/kg/day); the LOAEL was not established (>7000 ppm).

This dietary immunotoxicity study in the mouse is **Acceptable/Guideline** and satisfies the guideline requirement for an immunotoxicity study (OCSPP 870.7800) in the mouse.

A.4.9 Special/Other Studies

Non-guideline Comparative Thyroid Assay

Waived by HASPOC (H. DeLeon, TXR 0058198, 7/29/2021)

Appendix B. Physical/Chemical Properties

Table B.1. Physical/Chemical Properties of 9,10-Anthraquinone[1].

Parameter	Value	Reference
Molecular Weight	208.21 g/mol	--
pH	5.17 (as a 0.1% w/v aqueous dispersion	MRID 44496104
Water solubility (25°C)	1.75 mg/L	MRID 51479201 Acceptable Moderately soluble (FAO Classification Scheme)
Vapor pressure (25°C)	$1.16X10^{-7}$ mmHg	https://pubchem.ncbi nlm nih.gov/compound/Anthraquinone [Shimizu T et al; J Soc Dyers Colour 103: 132-7 (1987)] No guideline data submitted.
Dissociation constant, pKa	No dissociation between pH 2 - 10	--
Octanol/water partition coefficient, log K_{OW} (25°C)	3.39 at pH 7	https://pubchem.ncbi nlm nih.gov/compound/Anthraquinone (HSDB; experimental database value) No guideline data submitted.

1 Currently, there is no registered technical grade of the active ingredient (TGAI) for 9,10-anthraquinone.

Appendix C. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); the Agricultural Handler Exposure Task Force (AHETF) database; the Outdoor Residential Exposure Task Force (ORETF) database; the Agricultural Reentry Task Force (ARTF) database; ExpoSAC Policy 14.1 (SOPs for Seed Treatment); the Residential SOPs (lawns and turf), and a registrant-submitted exposure monitoring study (MRID 44339801) are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[24].

[24] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure