Responses to Public Comments and Peer Reviews

Imidacloprid Criteria Derivation Report

using the

Phase II: Methodology for Derivation of Pesticide Water Quality Criteria for the Protection of Aquatic Life in the Sacramento and San Joaquin River Basins

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Terms, Abbreviations, Acronyms, and Initialisms Potentially Used in this Report

Term	Definition
ACR	Acute to Chronic Ratio- used to estimate concentration that will protect against chronic toxicity
CDFG	California Department of Fish and Game
CVRWQCB	Central Valley Regional Water Quality Control Board
DPR	California Department of Pesticide Regulation
EC*x*	The chemical concentration that has an effect on *x*% of the test population.
Koc	Organic Carbon Partition Coefficient
LC50	The chemical concentration that is lethal to 50 % of the test population.
LOEC	Lowest Observed Effect Level- lowest concentration tested that has some effect on the test population
MATC	Maximum Allowable Toxicant Concentration -geometric mean of LOEC and NOEC
NOEC	No Observed Effect Level- highest concentration tested that has no effect on the test population
SSD	Species Sensitivity Distribution- Statistical probability distribution of toxicity data
UC Davis	University of California, Davis
US EPA	U.S. Environmental Protection Agency
Water Quality Objective (WQO)	The limits of water quality constituents or characteristics that are established for the reasonable protection of beneficial uses of water or the prevention of nuisance within a specific area.

1.0 Introduction

This document presents the responses to public comments and peer reviews received on a technical report prepared by the University of California at Davis, Environmental Toxicology Department, under contract (17-046-130) to the Regional Water Quality Control Board, Central Coast Region (Regional Board).

The imidacloprid criteria report was submitted to peer review, conducted by external scientific peer reviewers per the requirements of Health and Safety Code Section 57004.

The technical criteria report may be considered by the Regional Board in relation to a Board action, however, it does not represent Board Policy and is not regulation. The report is intended to generate numeric water quality criteria for the protection of aquatic life. However, these criteria should not be construed as water quality objectives. Criteria and guidelines do not have the force and effect of regulation, nor are they themselves water quality objectives.

2.0 Response to Comment to Public Comments

2.1. Comment Letter 1 – Sarah Hoyle, Aimee Code, Xerces Society for Invertebrate Conservation

COMMENT 1-1: The reviewed monitoring data from the Central Coast region on pages 20-21 of the draft document appears to be incomplete. Surface water monitoring data from the Department of Pesticide Regulation's Surface Water Database for 2010-2015 in the five counties noted (Monterey, San Benito (no samples), San Luis Obispo, Santa Barbara, and Santa Cruz) is summarized in Table 1. Sampling data shows that imidacloprid is often found in surface water throughout the region at levels that could cause harm to aquatic invertebrates. The monitoring data section in the final document should be revised to include all relevant samples from the region.

Table 1. Surface Water Imidacloprid Detections 2010-2015

County	# of Samples	# of Detections	Detection Frequency	Average Detection	High Detection
Monterey	218	178	82%	0.79 µg/L	6.8 µg/L
San Luis Obispo	24	17	71%	0.50 µg/L	1.12 µg/L
Santa Barbara	55	55	100%	1.62 µg/L	9.14 µg/L
Santa Cruz	9	4	44%	0.06 µg/L	0.07 µg/L

Response To Comment (RTC) 1-1: The detection data has been corrected for imidacloprid in Section 12.3.

COMMENT 1-2: We appreciate that mixtures were considered in the draft document, and encourage you to address them as criteria are developed for similar systemic insecticides, especially the other nitroguanidine neonicotinoids.

RTC 1-2: Comment acknowledged.

2.2. Comment Letter 2 – Sean McGee, Bayer CropScience LP

COMMENT 2-1: Imidacloprid has one of the most well characterized aquatic organism toxicity profiles of all insecticides. Thanks to vast product development and independent research efforts, a wealth of data from laboratory to environmentally relevant field studies are available for establishment of robust thresholds for protection of aquatic organisms of

interest (i.e. water quality criteria) and characterizations of potential risks associated with chemical detections from water monitoring programs. To date the aquatic toxicity database is comprised of >150 laboratory and >30 mesocosm studies covering ~28 taxa and providing more than 240 endpoints. The draft imidacloprid criteria provides a review of 41 of these studies. However, as discussed in the following paragraphs, because of methods used only 2 imidacloprid specific data points were used quantitatively for calculation of the acute and chronic criteria. Although it is unreasonable to expect all the data points to be appropriate for the derivations, incorporating more of this information into criteria derivation process would produce more accurate and robust criteria.

While the authors of the draft imidacloprid water quality criteria should be commended for their extensive efforts to identify relevant toxicity data, the UC Davis Methodology for Derivation of Pesticide Water Quality Criteria for the Protection of Aquatic Life (methodology) used to derive the criteria is inappropriate for selective compounds such as imidacloprid resulting in derivation of flawed criteria. Restrictions set forth by the methodology prevent leveraging of the wealth of data available for imidacloprid and rather than provide scientifically sound criteria, introduces uncertainty via omission of available robust and reliable scientific data. Data were excluded from criteria calculation on the basis of (1) adverse effects not being observed, (2) data generated with an imidacloprid formulation, and (3) acute and chronic data were not generated in the same test, by the same lab, or with the same dilution water. Additional uncertainty was introduced to the criteria with the safety factor and toxicity extrapolation techniques (e.g., acute-to-chronic ratio) used in place of relying on available quantitative study data. The following section will discuss the methodological issues in more detail followed by a section dedicated to technical corrections and recommendations for author consideration.

RTC 2-1: Comment acknowledged; specifics addressed below. See RTC 2-2, 2-3, and RTC 2-5.

COMMENT 2-2: Imidacloprid is considered a selective insecticide. Unlike legacy, more broad spectrum insecticides (e.g., chlorpyrifos) for which the UC Davis method (Methodology) was developed, sensitivity to imidacloprid is limited to particular pest and non-target taxa. For example, in the aquatic arena insects such as *Chironomus dilutus* (formally *C. tentans*) are sensitive to imidacloprid exposure while fish are insensitive with several studies unable to produce definitive (not greater than) LC50 or NOECs even when fish are exposed to imidacloprid at the limit of solubility. The Methodology was not designed for this selective nature as indicated by the requirement for definitive (uncensored) endpoints for a minimum of 5 different taxa including salmonid, warm water fish, planktonic crustacean, benthic crustacean and insect in order to meet the

criteria for the Species Sensitivity Distribution (SSD) approach to deriving criteria. For selective compounds it is not expected that definitive endpoints (acute LC/EC50 or chronic NOEC)will be obtained for all five taxa thereby eliminating the option of using an SSD and defaulting to an assessment (safety) factor approach regardless of the number of reliable studies available.

This is the case for imidacloprid. Despite the use of solvent (DMF) to assist dissolving technical imidacloprid in an acute warm water fish study submitted to EPA and CDPR (MRID 42055314), imidacloprid exposure at the limit concentration (defined by the limit of solubility) was not able to illicit sufficient toxicity to warm water fish to calculate an LC50. A lack of toxicity at the limit concentration was also observed in the chronic fish study (MRID 48671403) producing a NOEC greater than the highest test level. The highest treatment levels included in in the acute and chronic studies are approximately 4 orders of magnitude higher than the upper end of imidacloprid surface water detections in California. Testing above the limit of solubility is not an option as the material will precipitate, settle out and collect on the bottom of the test vessel. In this case, the exposure concentration defined by the analytical confirmation of imidacloprid in water remains at the solubility limit despite the additional material added. While there is no definitive endpoint, the imidacloprid data set does satisfy the purpose of the 5 taxa requirement, which is to ensure that toxicity information for a wide range of taxa, representing the full aquatic community, are available for deriving a water quality criteria.

RTC 2-2: The Methodology is not limited to concentrations related to previously detected environmental concentrations of any given pesticide. Environmental detections can change at any time. The UC Davis Method allows for studies that test pesticides at concentrations of up to twice their water solubility.

It is correct that studies exist that were performed on a breadth of taxa that satisfy the Methodology's requirements. However, the methodology instructs that only definitive toxicity values be used in the derivation of criteria (Table 3.8, TenBrook et al., 2009). Therefore, non-definitive values were not included. Studies that result in non-definitive values are included as supplemental data, as long as they meet other method requirements, such as use of technical or high purity materials (i.e., not a formulation).

COMMENT 2-3: Although there is no option for deriving a definitive (not greater than value) warm water fish endpoint and it is clear that the taxa are not sensitive to imidacloprid exposure, the methodology ignores the lack of sensitivity and defers the derivation of criteria to an assessment (safety) factor approach. The assessment factor (AF) approach relies on the lowest available RR rated endpoint and applies a "safety" factor to it

based on the assumption that taxa without suitable endpoints are more sensitive than available data predict. The approach is designed for compounds with very limited data, not imidacloprid which has one of, if not the, most robust aquatic toxicity data package of all insecticides. Further, this approach ignores all but the most sensitive acute endpoint and rather than acknowledge that warm water fish are insensitive, it implicitly assumes that the concentration defined by the lowest endpoint is not suitably low enough for protection of warm water fish.

RTC 2-3: The Assessment Factor approach used by the method is a conservative approach to ensure adequate protection for all aquatic species. It is up to regulators to determine the best use of the derived criteria based on location, pesticide use, and other contextual factors as appropriate.

COMMENT 2-4: A more flexible approach to how the current methodology is being applied should be considered for selective products which often have non-definitive endpoints for taxa required by the methodology due to lack of sensitivity. For imidacloprid we recommend quantitative criteria establishment efforts focused on the most sensitive taxa of interest (i.e., aquatic invertebrates) as documented in the scientific publications of Moore et al. 2016 and Whitfield-Aslund et al. 2017. The data for non-sensitive taxa would still be used, but in a qualitative manner, since they provide information to conclude that certain parts of the aquatic community are insensitive. If an SSD approach is used, the technical advantage of focusing exclusively on the most sensitive taxa is bi- and multimodal distributions of toxicity data are avoided resulting in a better curve fit to the toxicity data distribution and a more robust estimate of hazard concentrations. EPA's original 1985 Water Quality Criteria guidance essentially takes this approach since the actual regression to derive a criterion relies on just the 4 data point (typically the lowest values) around the desired criterion.

RTC 2-4: See RTC 2-2.

COMMENT 2-5: Restricting data for acute-to-chronic ratio (ACR) estimates to acute and chronic tests performed as part of the same study, in the same lab, or with the same dilution water is unnecessary and omits quantitative data deemed by the authors of the criteria as reliable. Studies rated by the authors as reliable followed appropriate testing methodologies, with many of the studies adhering to internationally recognized test guidelines (e.g., OECD or US EPA OCSPP guidelines) that have been inter and intra laboratory validated across the world, and therefore can be used for ACR calculations with confidence. Omitting these data, and relying instead on default ACR values defined by the

methodology does not result in water quality criteria based on the best available science. The authors should amend the methodology and use the reliable quantitative data available to ensure the water quality criteria are scientifically valid and robust.

RTC 2-5: Section 3-4.2 of the method (TenBrook et al., 2009) describes the ACR procedure in detail. This ACR procedure was followed for the derivation of the chronic criterion for imidacloprid.

COMMENT 2-6: Wildlife dietary values and bioaccumulation potential for animals with significant food sources in water (pg 9 and 16-18):
Two hen metabolism (MRID 42556116, 42556117) and rat metabolism studies (MRID 42256356) are available to address ADME and potential for bioaccumulation. The rapid depuration of imidacloprid observed in these studies demonstrates bioaccumulation is not a concern for terrestrial vertebrates.

RTC 2-6: The Methodology only accounts for aquatic species; therefore, non-aquatic species such as rats and chickens are not considered in the report.

COMMENT 2-7: Lack of acceptable mesocosm studies (pg 10):
Over thirty-five microcosm and mesocosm (cosm) studies investigating potential impacts of imidacloprid exposure on aquatic invertebrates or aquatic communities are available. These studies are representative of the potential exposure and impacts in the environment from product use and as such often use formulated products for the investigation to mimic actual use conditions. As these studies are designed to be more environmentally relevant and have a lower degree of uncertainty associated with extrapolation from laboratory studies to the field, the methodology should be revised to consider data from relevant formulated studies and not only studies performed with the technical material.

RTC 2-7: Most of the mesocosm studies located during the literature search for imidacloprid used formulations. The draft report has been revised to state that two mesocosm studies that used high purity imidacloprid were identified; one was deemed not relevant/reliable and the other rated highly and was therefore incorporated into the report. Note that mesocosm studies are only used to compare to the chronic criterion to ensure that the chronic criterion is protective on any effects observed in mesocosm studies.

COMMENT 2-8: However, even under current restrictions Moring et al. 1992 (MRID 42256306) should be used for the imidacloprid water quality criteria derivation as this high quality study was performed with technical

imidacloprid and reports a NOEC of 6 µg ai/L based on observed recovery.

RTC 2-8: The Moring et al. 1992 study has been added to the report.

3.0 Response to Comment to Peer Reviews

3.1. Peer Review 1 – Christian H. Krupke, Department of Entomology, Purdue University

REVIEW 1-1: In terms of assumptions implicit in this conclusion, I note the following: It is reasonable and appropriate to focus upon animals vs. plants here. The principle is sound, in that acute criteria cannot reasonably be assessed using aquatic plants and alga.

Response to review (RTR) 1-1: Comment acknowledged.

Review 1-2: The balance of the analysis is based upon determination of an assessment factor, because data from only four (and not the required five, no warm water fish dataset was available) taxa are available to develop a statistical distribution. I find the use of an assessment factor to be a valid approach in the absence of abundant primary acute toxicity literature, with one caveat: development of the past assessment factors all are based upon pesticides (organochlorines, organophosphates, pyrethroids) that are (in general) orders of magnitude less soluble in water than imidacloprid and this gives me pause in comparing approaches directly. The assumption implicit in using the same approach is that the primary data are comparable. I am not aware of whether the work with older pesticide classes quantified the aqueous concentrations of these compounds rigorously (i.e. before, during and after the assays), or ensured that the materials stayed in solution so that organisms in the tests received a known dose. In the case of imidacloprid, it is clear that the authors screened for this factor in their literature assessments, judging by the notes/tables presented at the end of the document (i.e. nominal vs. measured concentrations are a measure assessed for generating reliability score).

RTR 1-2: The assessment factor procedure is presented in Section 3-3.3 of the method (TenBrook et al. 2009) and its development is discussed in Section 2-3.2 of TenBrook et al. 2006.

Review 1-3: There is an assumption made in development of the acute criterion that, following the estimation of a 5th percentile acute toxicity value, dividing by 2 will result in an acceptable “no effect level”. I was not able to readily find the justification for this calculation, although I certainly agree that dividing that final acute value by some factor is appropriately conservative, I was not able to determine why this value was chosen in my reading of the document.

RTR 1-3: Dividing by 2 is a safety factor that allows for an additional buffer for a more conservative criterion determination.

Review 1-4: The ostracod mentioned here is frequently mentioned in other work (i.e. from Holland and Switzerland in the EU) as a highly sensitive invertebrate species to base water quality criteria upon and the literature base for this ostracod is rigorous. As there are not new, and more representative, data featuring CA freshwater species available, there appear to be no options for further refinement at this time. This is sound methodology and I note that it was considered in development of the acute toxicity criterion. The notes/tables in the literature review section include whether test organisms are native or not. As a side note, the reported value for this species of 0.07 microgram/L is low, in terms of environmental concentrations reported, and this lends confidence that the criterion is likely to be environmentally valid. In addition, this ostracod species is more sensitive to imidacloprid (broadly speaking) than the EPT (Ephemeroptera, Plecoptera, Trichoptera) insect taxa commonly used as environmental quality indicators. In sum, I find that this conclusion is based upon sound scientific knowledge, methods and practices.

RTR 1-4: Comment acknowledged.

Review 1-5: As with the development of the acute criterion, a shortage of appropriate data precluded the development of a statistical distribution upon which chronic criteria could be based. The development of the chronic criterion relies upon two crustacean species, one freshwater and one saltwater. For both, a species mean acute to chronic ratio (SMACR) was calculated. The freshwater species used is Daphnia magna, (SMACR = 34), which I note here is known to be orders of magnitude more tolerant of certain neonicotinoids (i.e. clothianidin) than some insects that are likely to be exposed in freshwater (for example, larvae of Chironomus sp midges. Further, the chronic study for the other available species, M. bahia, demonstrated indications of acclimation (i.e. the chronic toxicity value is far higher than the acute value, which makes little sense). Therefore, a default acute-to-chronic ratio (2.0) was used for this species. This adjustment is reasonable and appropriate.

RTR 1-5: Comment acknowledged.

Review 1-6: Before calculation of a geometric mean, these ratios are combined with a “default chronic acute to chronic ratio” of 11.4; it was not immediately apparent to me where this default value came from in this case, and I assume it is a “global mean” generated from the primary literature.

RTR 1-6: The method provides a default ACR value when a lack of original data exists. See section 3-4.2.3 of the method (TenBrook et al. 2009). The method allows for updates to this default value should additional relevant data become available. In 2014, the sediment method updated the default ACR value to be used in both aquatic and sediment calculations to be 11.4 (see Section 3.6.3 of Fojut et al. 2014 and Section 1 of the imidacloprid draft report).

Review 1-7: Following the calculation using these three SMACR values, the resulting chronic toxicity value is 0.014 microgram/L, or 14 ng/L. This is approximately 5-fold below the acute criterion presented earlier in the document. I note here again that with D. magna, a relatively tolerant species to neonicotinoids included in the calculation, there is potential to bias this estimate upward (i.e. be less conservative).

RTR 1-7: Comment acknowledged.

Review 1-8: Given the limitations of the data however, I do find that the calculation is based on sound scientific principles.

RTR 1-8: Comment acknowledged.

Review 1-9: In the sections that I reviewed (conclusions 3 and 4), the selection of primary literature to include was exceptionally rigorous, resulting in only the highest quality data being used for subsequent calculations. However, the calculated chronic value is a challenge to assess, because I found certain scientific issues (as related to real world exposure), unaddressed. These include: 1) because imidacloprid is most heavily used in agricultural and homeowner pest management in terrestrial systems, most exposed organisms are likely to be freshwater species, and 2) most exposed aquatic organisms are likely to be insects, and not crustaceans. The only two acceptable datasets come from crustaceans, one of them a saltwater species. This gives me some pause in evaluating that recommendation, simply because no acceptable data were available for the large group of organisms (freshwater insects) at most risk of chronic exposure.

RTR 1-9: Comment acknowledged. If additional highly rated data for freshwater aquatic insects become available in the future, they should be incorporated into the chronic criterion calculation.

Review 1-10: I make these statements with the realization that chronic data are among the most difficult to generate for terrestrial animals. They are even more difficult to generate for aquatic animals interacting with a water-soluble pesticide, in that the organisms are constantly “soaking in it”, and there may be no refuge, or return to zero, at any time in their environment, a contrast with some older pesticide classes. Furthermore, water solubility adds the possibility that pulses of insecticide (for example as runoff from agricultural drainage) are likely to be far more common than a consistent/constant exposure level for any period of time; whereas this latter scenario is a cornerstone of chronic exposure studies. None of this negates or reduces the urgency to develop chronic toxicity guidelines for a virtually ubiquitous insecticide like imidacloprid, but I think it is important for these caveats to be entered into the public discourse as priorities for future research.

I commend the state of California and the team that assembled the water quality criteria report for imidacloprid for being the first in the country to take on the thorny regulatory issue of neonicotinoids in water. This class of insecticides owes part of their popularity to their exceptionally high water solubility – orders of magnitude higher than many of our older insecticide classes. This means they can be applied on seeds, into and near roots, and into irrigation water and be taken up and into the plant. This water solubility, while beneficial for some pest management considerations, makes managing these compounds somewhat problematic once they leave the target area or plant, which a burgeoning literature base tells us they do. Neonicotinoids have rapidly (primarily over the last 10-15 years or so) become the leading agricultural insecticide class in the country, with imidacloprid, thiamethoxam, and clothianidin all being applied over tens of millions of acres annually in virtually every cropping system, as well as many residential/homeowner applications. Although there are guidelines in place or being developed in the EU and Canada, the US lags well behind, despite using far more of these compounds per unit area than any other country. In other words, the acute and chronic criteria derivations are important.

RTR 1-10: Comment acknowledged.

3.2. Peer Review 2 – Francisco Sánchez-Bayo, The University of Sydney, Australia

REVIEW 2-1: The physical-chemical data was gathered mainly from scientific reports by the manufacturer, a few databases and reference books as well as several publications in the scientific literature. The information presented in the Draft is correct, but for a couple of minor errors: Page 5: the Henry's constant geometric mean (5.8×10^{-12} Pa m^3 mol^{-1}) is incorrectly estimated from the three values shown: the correct value is 2.68×10^{-9} Pa m^3 mol^{-1}.

RTR 2-1: The geometric mean of the Henry's Law Constant has been recalculated.

REVIEW 2-2: Page 7: in Table 1 (Bioconcentration factors), the study by Paraiba 2008 refers to modelling in potatoes, and this should be indicated under the 'species' column. Also, average values for the fish Australoheros facetus (Iturburu 2017, Table 1) should be 1.0, 0.7, 0.6, 0.6, 0.5 and 0.3; all BCF values for this fish are from a formulation tested under static conditions.

RTR 2-2: The Paraiba value and reference has been removed.

REVIEW 2-3: Page 8: Table 2 contains information from very old references and is clearly incomplete. Although the data presented are correct, this table should be updated and include new data from field and

laboratory studies; although this information is not pertinent to the determination of aquatic benchmarks, it is important for the risk assessment of this compound, which is the main practical use of this Water Quality Criteria Report. Suggest including in this table the following data:

Hydrolysis: 20 d (pH 10.8) and 2.85 d (pH 11.8) as determined by Zheng & Liu 1999. Kinetics and mechanism of the hydrolysis of imidacloprid. Pestic. Sci. 55, 482-485.

Aqueous photolysis:
1. half-life of 0.314 hours in deionized water, as determined by Lavine et al. 2010. LCPDA- MS studies of the photochemical degradation of imidacloprid. Anal. Lett. 43, 1812-1821.

2. half-life of 2.3 hours in aqueous solution, reported by Kurwadkar et al. 2016. Modeling photodegradation kinetics of three systemic neonicotinoids—dinotefuran, imidacloprid, and thiamethoxam—in aqueous and soil environment. Environ. Toxicol. Chem. 35, 1718-1726.

Soil photolysis: half-life of 830 h in dry soil, determined by Graebing & Chib 2004. Soil photolysis in a moisture- and temperature-controlled environment. 2. Insecticides. J. Agric. Food Chem. 52, 2606 -2614.

Soil degradation:
1. half-lives of 990 d (red brown earth), 1080 d (quarry sand) and 1230 d (sanddolomite) in dry soils, reported by Baskaran et al. 1999. Degradation of bifenthrin, chlorpyrifos and imidacloprid in soil and bedding materials at termiticidal application rates. Pestic. Sci. 55, 1222-1228.
2. half-lives of 50 -132 d in soils, reported by Broznić & Milin 2013. Mathematical prediction of imidacloprid persistence in two Croatian soils with different texture, organic matter content and acidity under laboratory conditions. J. Environ. Sci. Health B 48, 906-918.

RTR 2-3: These values and references have been added to the draft report.

REVIEW 2-4: The screening performed is adequate but stringent, as it excluded some data points and species that did not comply with the evaluation criteria established in the methods (TenBrook et al. 2009). Most of the reasons given for exclusion, however, are reasonable (e.g. short duration of the tests, inexact derived value) and justified, while others (e.g. not a standard test method, or chemical purity not reported) seem unjustified to me because they tend to exclude data that are very likely trustworthy.

RTR 2-4: Comment acknowledged.

REVIEW 2-5: For determination of the acute criterion this strict selection prevented the analysis of a species sensitivity distribution that would have been preferable to the Assessment Factor (AF) procedure used. Nevertheless, the latter method is considered adequate and valid.

RTR 2-5: Comment acknowledged.

REVIEW 2-6: However, such a reduction of data may have hampered the estimation of an accurate chronic criterion, which was restricted to consider data only from two species, one of which (Daphnia magna) is notoriously insensitive to this compound – see Morrissey et al. 2015, Neonicotinoid contamination of global surface waters and associated risk to aquatic invertebrates: a review. Environ. Int. 74, 291-303.

For the chronic criterion the data by Roessink et al. 2013 and van den Brink et al. 2016 are deemed essential, but these and other relevant work on toxicity have been omitted. See below a number of relevant publications that should be consulted for the estimation of both the acute and chronic benchmarks:

• Alexander, A.C., Culp, J.M., Liber, K., Cessna, A.J., 2007. Effects of insecticide exposure on feeding inhibition in mayflies and oligochaetes. Environ. Toxicol. Chem. 26, 1726-1732.
• Bottger, R., Schaller, J., Mohr, S., 2012. Closer to reality - the influence of toxicity test modifications on the sensitivity of Gammarus roeseli to the insecticide imidacloprid. Ecotoxicol. Environ. Saf. 81, 49-54.
• Chen, X.D., Culbert, E., Hebert, V., Stark, J.D., 2010. Mixture effects of the nonylphenyl polyethoxylate, R-11 and the insecticide, imidacloprid on population growth rate and other parameters of the crustacean, Ceriodaphnia dubia. Ecotoxicol. Environ. Saf. 73, 132-137.
• Kreutzweiser, D., Good, K., Chartrand, D., Scarr, T., Thompson, D., 2007. Non-target effects on aquatic decomposer organisms of imidacloprid as a systemic insecticide to control emerald ash borer in riparian trees. Ecotoxicol. Environ. Saf. 68, 315-325.
• Kreutzweiser, D.P., Good, K.P., Chartrand, D.T., Scarr, T.A., Thompson, D.G., 2008. Toxicity of the systemic insecticide, imidacloprid, to forest stream insects and microbial communities. Bull. Environ. Contam. Toxicol. 80, 211-214.
• LeBlanc, H.M.K., Culp, J.M., Baird, D.J., Alexander, A.C., Cessna, A.J., 2012. Single versus combined lethal effects of three agricultural insecticides on larvae of the freshwater insect Chironomus dilutus. Arch. Environ. Contam. Toxicol. 63, 378-390.

• Roessink, I., Merga, L.B., Zweers, H.J., van den Brink, P.J., 2013. The neonicotinoid imidacloprid shows high chronic toxicity to mayfly nymphs. Environ. Toxicol. Chem. 32, 1096-1100.
• Song, M.Y., Stark, J.D., Brown, J.J., 1997. Comparative toxicity of four insecticides, including imidacloprid and tebufenozide, to four aquatic arthropods. Environ. Toxicol. Chem. 16, 2494-2500.
• van den Brink, P.J., Smeden, J.M.V., Bekele, R.S., Dierick, W., Gelder, D.D., Noteboom, M., Roessink, I., 2016. Acute and chronic toxicity of neonicotinoids to nymphs of a mayfly species and some notes on seasonal differences. Environ. Toxicol. Chem. 35, 128-133.

RTR 2-6: Morrissey et al. 2015 is a review and was not included because the method relies on original studies only. Song et al. 1997, LeBlanc et al. 2012, Kreutzweiser et al. 2007 and 2008, Chen et al. 2010, Alexander et al. 2007, Roessink et al. 2013, and Van de Brink et al. 2016 utilize imidacloprid formulation and were therefore not included in the report. The method requires that technical grade or high purity pesticides be used. Bottger et al. 2013 was rated as not relevant and was not included reviewed in the report. However, the report has been updated to make not of its existence in Section 10.2 Further, Kreutzweiser et al. 2007 did not utilize direct application of the pesticide to the waterbody but rather the secondary leaching effect of imidacloprid from treated terrestrial leaves and from soil. It was therefore deemed not relevant and was not included in the report.

REVIEW 2-7: The calculated acute and chronic criteria (0.07 µg/L and 0.014 µg/L, respectively) are scientifically sound and valid based on the methodology used; they are comparable to those derived in other jurisdictions, and this adds confidence in their determination. They are protective of threatened or endangered species and freshwater ecosystems in California and probably elsewhere.

RTR 2-7: Comment acknowledged.

REVIEW 2-8: In regard to water quality effects (Section 9), the studies by Ding et al. 2004 and Iturburu et al. 2017 specifically refer to bioavailability and bioconcentration of imidacloprid in fish kept in aquaria, so unless I am missing something the statement “No studies were found concerning the bioavailability of imidacloprid to organisms in the water column” (p. 13) is incorrect.

RTR 2-8: Section 9.1 has been updated to include a discussion of these two studies.

REVIEW 2-9: I was also surprised to read that “No acceptable mesocosm, microcosm or ecosystem (field and laboratory) studies were identified” (p. 15). I am of the opinion that these studies cannot be screened using the same reliability criteria used for acute and chronic laboratory studies. The fact is there are at least 15 microcosms and mesocosm available in the public literature, the most recent being Rico et al. 2018 (Effects of imidacloprid and a neonicotinoid mixture on aquatic invertebrate communities under Mediterranean conditions. Aquat. Toxicol. 204, 130-143). Some of those studies may not be reliable, but I very much doubt than none of them are acceptable or pertinent. For example, Smit et al. (2015) used 6 of these studies to evaluate the toxicity to freshwater ecosystems, although these authors used the method of De Jong et al. (2008) to screen the available data, not the method of TenBrook et al. 2009.

RTR 2-9: Most of the mesocosm studies located during the literature search for imidacloprid used formulations. The draft report has been revised to state that two mesocosm studies that used high purity imidacloprid were identified; one was deemed not relevant/reliable and the other rated highly and was therefore incorporated into the report. Note that mesocosm studies are only used to compare to the chronic criterion to ensure that the chronic criterion is protective on any effects observed in mesocosm studies.

REVIEW 2-10: Indeed, the assumptions, limitations and uncertainties used by the authors followed a well-defined and valid method (TenBrook et al. 2009) that provides full confidence in the derived criteria. As mentioned above, I think this screening method resulted in the exclusion of some studies reporting reliable data, thus preventing the use of SSD methods for the calculation of the acute criterion, while the chronic data was reduced to a minimum of two species, even if reliable data for more species exists. However, the applied methodology is certainly robust and the resulting criteria are accurate and acceptable.

RTR 2-10: Comment acknowledged.

REVIEW 2-11: A final comment: a reference should be cited regarding the environmental monitoring data for the State of California, which is described in detail in pp. 20-21. Suggestion: Starner and Goh, 2012. Detections of the neonicotinoid insecticide imidacloprid in surface waters of three agricultural regions of California, USA, 2010–2011. Bull. Environ. Contam. Toxicol. 88, 316-321.

RTR 2-11: Comment acknowledged.

REVIEW 2-12: One issue very relevant to the chronic criterion is the delayed mortality observed with aquatic invertebrates exposed to

imidacloprid over long periods. This unusual toxic behaviour has been reported by several authors, including myself, and basically results in acute/chronic ratios of LC50s much greater than 10 (it is 34 for D. magna), which can be as large as 800 for mayfly nymphs after 4 weeks exposure (Sanchez-Bayo et al. 2016, Contamination of the aquatic environment with neonicotinoids and its implication for ecosystems. Front. Environ. Sci. 4, 71). By contrast, it is noted that the acute and chronic criteria derived here differ only by a factor of 5, whereas a larger factor of 24 is found between acute and chronic benchmarks derived for Europe (Smit et al. 2015).

RTR 2-12: The studies used in the draft report for the acute-to-chronic ratio calculations use data from studies that meet the method requirements. Sanchez-Bayo et al. 2016 paper referenced in Review 2-11 is a review paper and the acute-to-chronic ratio values referenced therein come from studies that did not meet the requirements of the method. For example, Roessink et al. 2013 utilized a formulation and Sanchez-Bayo et al. 2009 is a prediction modeling study utilizing published data. Smit et al. 2015 is also a review paper that does not contain original data.

REVIEW 2-13: A section discussing this point would be worth including, because it is pertinent to the derivation of the chronic criterion. A recent publication explaining this point is: Pisa et al., 2017. An update of the Worldwide Integrated Assessment (WIA) on systemic insecticides. Part 2: Impacts on organisms and ecosystems. Environ. Sci. Pollut. Res. doi: 10.1007/s11356- 017-0341-3.

RTR 2-13: A discussion of delayed mortality and issues of acute mortality as an estimate of toxicity specifically for imidacloprid has been added to section 12.1 of the draft report.

REVIEW 2-14: Yes, the methods used are valid and scientifically sound, and the resulting criteria are
trustworthy.

RTR 2-14: Comment acknowledged.

3.3. Peer Review 3 – Els Smit, National Institute of Public Health and the Environment Centre for Safety of Substances and Products Bilthoven, the Netherlands

REVIEW 3-1: Overall, the physico-chemical data as summarised in the report are adequate for the purpose of the assessment. In general, I would recommend only to use secondary sources such as the PPDB or Tomlin's Pesticides Manual in the absence of other reliable sources. In this case, the original regulatory assessments may be used instead. Please refer to section 2.2 of this review for specific comments.

RTR 3-1: Comment acknowledged.

REVIEW 3-2: It is not clear if the literature search resulted in a complete list of potentially relevant studies. I could not find reference to studies that were critical in recent EU regulatory assessments, water quality standard derivations and literature reviews of imidacloprid.

RTR 3-2: The literature review followed the guidelines in the Method. Literature sources included peer review journals, studies listed in various federal US agency databases, as well as studies submitted to government agencies in the United States for pesticide registration and/or re-registration. See section 3-2.1 of TenBrook et al. 2009.

REVIEW 3-3: It is stated that no acceptable microcosm studies were identified in the literature, but information is missing on which studies were retrieved and if/how they were evaluated. Multiple micro- and mesocosm studies are available in the literature so it is advised to add more information.

RTR 3-3: Most of the mesocosm studies located during the literature search for imidacloprid used formulations. The draft report has been revised to state that two mesocosm studies that used high purity imidacloprid were identified; one was deemed not relevant/reliable and the other rated highly and was therefore incorporated into the report. Note that mesocosm studies are only used to compare to the chronic criterion to ensure that the chronic criterion is protective on any effects observed in mesocosm studies.

REVIEW 3-4: It is advised that the additional references indicated in section 2.4 of this review are checked for additional relevant literature. See reference list for details.

RTR 3-4: See RTR 2-11.

REVIEW 3-5: The scoring system is quite strict and it's my impression that the focus is on NOECs instead of EC10 values. This may result in a bias towards guideline studies with standard test species. Studies with non-standard species are often not as well reported as guideline studies and are more likely to have reliability points taken off. As there is a tendency in ecotoxicological literature to report EC10-values instead of NOECs, scientifically valid studies may be missed. Recent European guidance documents use NOEC and EC10 interchangeably.

RTR 3-5: Section 3-2.1.2 of the method states that "Chronic data expressed as ECx values (from regression analysis), may be used for criteria derivation only if studies are available to show what level of x is appropriate to represent a no-effect level."

REVIEW 3-6: The evaluation method results in small acute and chronic datasets with <5 species. Therefore, SSDs cannot be used and the AF-method (acute) and the ACR-method (chronic) are used. It is questionable, however, if a generic ACR-method is applicable to imidacloprid. The ACR of imidacloprid for insects is highly variable and may span several orders of magnitude.

RTR 3-6: Comment acknowledged.

REVIEW 3-7: Potentially relevant species that are not included in the chronic data set, will not be taken into account in the ACR either. Even accepted chronic studies may not be included in the ACR if a valid acute endpoint for the same species is not available. Similarly, potentially sensitive species for which only acute data are available are not included in the ACR either.

The absence of sensitive non-standard test species in the dataset and ACR is very important for imidacloprid (and other neonicotinoids), because it is demonstrated that other aquatic taxa are much more sensitive to imidacloprid than the standard test species.

RTR 3-7: Comment acknowledged. Should additional acute and chronic data become available for non-standard aquatic species that are particularly sensitive to imidacloprid that could be used for ACR calculations, they should be incorporated into the report.

REVIEW 3-8: The evaluation criteria are transparent and applied in a consistent way and as such the evaluation is in agreement with the UC Davis aquatic method. The report would benefit from a discussion on the suitability of the evaluation method for neonicotinoids and other compounds for which sensitivity of non-standard test species is high.

Despite these fundamental issues, the resulting acute and chronic criteria seem to be in line with those derived in European regulatory assessment for biocides and plant protection product, and national quality criteria derived in the Netherlands, Germany and Switzerland (see further below).

RTR 3-8: Comment acknowledged.

REVIEW 3-9: The acute criterion is derived according to the methodology by first dividing the lowest acute toxicity value of 1 µg/L for *Cypretta seuratti* by an AF of 7.5, and then by an AF of 2. The combined AF is 15. It is stated that "Using an assessment factor is a conservative approach for calculating the imidacloprid acute criterion, which is reasonable because so little acute toxicity data is available for this pesticide." I do not agree with the statement that little acute toxicity data is available, in my opinion this is partly a result of the strict scoring system.

The Dutch acute quality criterion is based on a lower EC50 of 0.65 µg/L for *Epeorus longimanus*. The underlying study from Alexander et al. (2007) is not listed in the references.

RTR 3-9: The study "Alexander AC, Culp JM, Liber K, Cessna AJ. 2007. Effects of insecticide exposure on feeding inhibition in mayflies and oligochaetes. Environ Toxicol Chem 26, 1726-1732" was determined not to be relevant according to the method because it utilized a pesticide formulation rather than technical grade or high purity material.

REVIEW 3-10: It is noted that the derived acute criterion of 0.07 µg/L is still lower than those from Switzerland and Germany (0.1 µg/L, EC50 *C. seuratti* with AF 10; Oekotoxzentum, 2016; Wenzel & Shemotyuk, 2014) and the Netherlands (0.2 µg/L, based on mesocosm data; Smit, 2014; Smit et al., 2015). Note that the Swiss derivation method does not take into account studies with formulations.

RTR 3-10: The referenced studies by Oekotoxzentum, 2016; Wenzel & Shemotyuk, 2014 were not able to be located to determine their relevance to this comment and report. Smit 2014 and 2015 are review papers that do not contain original data.

REVIEW 3-11: In conclusion: The derivation of the acute criterion is in line with the UC Davis aquatic method. The fact that lower acute ecotoxicity values may be present in the literature is compensated for by the higher assessment factor.

RTR 3-11: Comment acknowledged.

REVIEW 3-12: The chronic criterion is calculated from the recommended acute value (=EC50/7.5) by applying a geometric mean acute-to-chronic ratio of 9.19, based on the ACR for *Daphnia magna* (34), the saltwater mysid *Mysidopsis bahia* (2), and a default ACR (11.4). It is stated that "Using an acute-to-chronic ratio procedure is a conservative approach for calculating the imidacloprid chronic criterion, which is reasonable because so little acute toxicity data is available for this pesticide." As indicated above, in my opinion more valid acute toxicity data are available.

RTR 3-12: Comment acknowledged.

REVIEW 3-13: The ACR of *Mysidopsis* (*Americamysis*) *bahia* study should be checked. The MATC values from two tests for growth are reported in the main text as 3,806 and 230 µg/L (geomean 935 µg/L), but the datasheet for the Ward 1991-study gives 3806 and 230 **ng/L** (→ geomean 935 ng/L → SMACR = 38). If I'm correct, the final geometric mean multispecies ACR would then be 24.5, and the chronic criterion would become 0.0029 µg/L (2.9 ng/L). In my opinion, the large difference between the two *M. bahia* tests should be discussed. It is further noted that the MATC for reproduction is lower (849 ng/L). This would lead to a higher SMACR.

RTR 3-13: The units for the MATC values for growth have been updated in Section 8 of the report to be ng/L rather than µg/L. This results in an update to the *M. bahia* SMACR for growth = 38.4 µg/L.

The report has been updated to utilize the lower MATC value for reproduction in the calculation of the *M. bahia* SMACR as well as the final chronic criterion. The updated value is 5.1 ng/L, or less than half of what it was originally calculated to be.

REVIEW 3-14: The ACR of imidacloprid for insects is highly variable and may span several orders of magnitude. In the dataset that was used for deriving quality standards in the Netherlands, ACRs ranged from 16 for *Chironomus tentans* to 143 for *Chaoborus obscuripes* (median 39, geometric mean 47), and even higher values are mentioned in the literature. The ranking of individual species as regards their relative sensitivity differs between acute and chronic studies, and a straightforward extrapolation from the acutely most sensitive endpoint is difficult. It is advised to discuss the applicability of an ACR based on standard test species and to motivate that the ACR of notoriously insensitive species such as D. magna can be used. In my opinion, it would be better to rely on chronic data, provided that NOEC/EC10-values for sensitive non-standard test species (e.g., mayflies) are included.

RTR 3-14: ACR procedures in the UC Davis method are not based on standard test species. The procedures utilize highly rated studies that meet the method guidelines (e.g., ideally acute and chronic data originating from the same study/water/laboratory but allowances are made for data that originate from different studies/waters/laboratories). If highly rated acute and chronic data for more sensitive species become available that meet the method guidelines for data quality and ACR procedures, then the report should be updated.

REVIEW 3-15: Despite these considerations, the final chronic criterion (now 14 ng/L, but probably 2.9 ng/L) is in line with European regulatory values and water quality standards:

- EU biocides 4.8 ng/L (EC10 with AF 5; EC, 2015),
- EU plant protection products 9 ng/L (HC5 27 ng/L with AF 3; EFSA, 2014b)
- Netherlands 8.3 ng/L (HC5 25 ng/L with AF 3; Smit et al., 2015),
- Switzerland 13 ng/L (NOEC 0.67 µg/L for Chironomus tentans with AF 50; Oekotoxzentrum, 2016)
- Germany 2.4 ng/L (EC10 24 ng/L for Caenis horaria with AF 10; Wenzel & Shemotyuk, 2014).

RTR 3-15: The chronic value has been recalculated as 16 ng/L.

REVIEW 3-16: In conclusion: In principle, the derivation of the chronic criterion is in line with the UC Davis aquatic method, but the SMACR for *M. bahia* should be checked. There are methodological issues of which the applicability of the ACR is most prominent. It is advised that this is discussed in the report. However, according to my knowledge on ecotoxicity data for imidacloprid, the proposed chronic criterion may still be protective.

RTR 3-16: Comment acknowledged.

REVIEW 3-17: It is agreed that in view of the physico-chemical characteristics, there is no need to adjust the criteria regarding bioavailability. Distribution to the food chain and/or other environmental compartments is not relevant.

Mixture toxicity is an important issue, but this would require a thorough investigation into other neonicotinoids. Note that the list of neonicotinoids is longer than those mentioned in the report.

As indicated above, multiple micro- and mesocosm studies are available in the literature, it is advised to add information on which studies were retrieved and if/how they were evaluated.

RTR 3-17: The report has been updated to include a highly rated mesocosm study that utilized high purity imidacloprid. Note that mesocosm studies are only used to compare to the chronic criterion to make sure the chronic criterion is protective on any effects observed in mesocosm studies.

> **REVIEW 3-18:** The generally accepted CAS is 138261-41-3. This number is used in all official European reviews and databases (https://echa.europa.eu/brief-profile/-/briefprofile/100.102.643) and is used by the main European supplier BAYER.

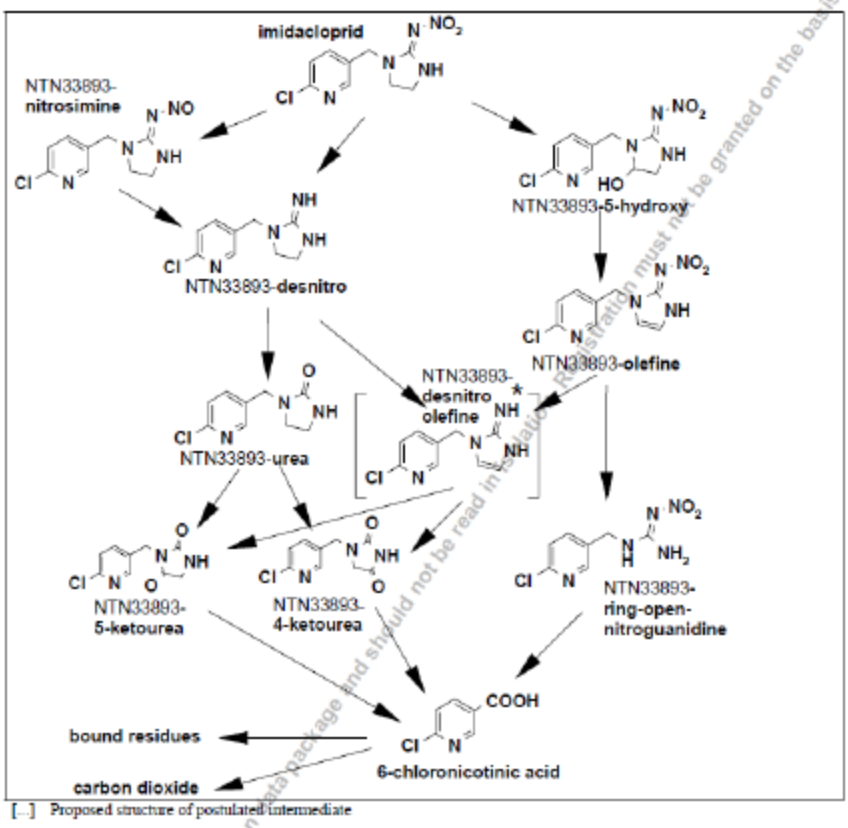
RTR 3-18: For transparency, the report retains both CAS numbers as they are both encountered in United States databases.

> **REVIEW 3-19:** IUPAC name is (2E)-1-[(6-chloropyridin-3-yl)methyl]-Nnitroimidazolidin-2-imine.

RTR 3-19: The report has been updated to include the IUPAC name found on the United States National Library of Medicine's PubChem website for CAS number 138261-41-3.

> **REVIEW 3-20:** Consider to present the degradation pathway as part of the environmental fate section. Slightly different schemes are presented in the European assessment of imidacloprid as plant protection product (EC, 2006; part B.8).

Figure B.8.1-1: Proposed metabolic pathway for the aerobic degradation in soil of imidacloprid



[...] Proposed structure of postulated intermediate

RTR 3-20: Comment acknowledged.

REVIEW 3-21: General comment: PPDB is a secondary source which extracts data from a.o. European regulatory assessments. I would advise to take the data from the original assessments, and use PPDB (and Tomlin's pesticide manual) only if no other source is available. Peer reviewed data on physico-chemical data can be found in the list of endpoints prepared in the context of the European assessment of imidacloprid as plant protection product and biocide. See Appendix 1 in EFSA (2008) and EC (2015).

RTR 3-21: Comment acknowledged. PPDB values have been removed when other values are available.

REVIEW 3-22: Water solubility
data in EFSA (2008):
613 mg/L (demineralised water, pH 5.5, 20 °C),
607 mg/L (pH 4, 20 °C)
601 mg/L (pH 9, 20 °C) (99.9 % for all)

independent of the pH in the range between 4 and 9.

RTR 3-22: These values have been added.

REVIEW 3-23: Vapor pressure data in EFSA (2008):
20 °C: 4 x 10-10 Pa; 25 °C
9 x 10-10 Pa
extrapolated from measurement between 50 to 70 °C (99.9 %)
I got slightly different results when running EpiSuite (version EpiWeb 4.1):
VP (Pa, 25 deg C) : 0.000225 (Modified Grain method)

EpiSuite values should not be included twice in the geometric mean.

Dissociation constant pKa
See previous comment on PPDB, prefer to use EFSA (2008) and EC (2015).

RTR 3-23: These values have been added/updated.

REVIEW 3-24: Henry's law constant: State temperature
See previous comment on PPDB, prefer to use EFSA (2008) and EC (2015): 1.7 * 10-10 Pa m3 mol-1 (20 °C)
EpiSuite gives an experimental database match: 1.67E-010 Pa-m3/mole. This is probably the same value as in EFSA (2008) and EC (2015).

RTR 3-24: Temperatures have been added and the EFSA value has been added.

REVIEW 3-25: Organic Carbon Sorption Partition Coefficients (log Koc)
EFSA (2008) gives values for 12 soils. It's not appropriate to calculate geometric mean of the log-values, either use the geometric mean of the untransformed data, or the arithmetic mean of the logtransformed data.

RTR 3-25: This has been updated.

REVIEW 3-26: log Kow
See previous comment on PPDB, the value of 0.57 is taken from EFSA (2008). Tomlin and Kidd most likely refer to the same study, both are secondary sources.

RTR 3-26: The reference has been updated.

REVIEW 3-27: Bioconcentration factor

Both EpiSuite values are modelled using log Kow 0.57. PPDB value is also modelling result, but the origin of the QSAR is not clear

RTR 3-27: Comment acknowledged.

REVIEW 3-28: Environmental fate
Consider to make this a separate section, because Fate and behaviour are usually not considered as being physico-chemical data. Alternatively adapt the heading to include environmental fate.

RTR 3-28: Comment acknowledged.

REVIEW 3-29: DT50 hydrolysis 355 d is most likely an extrapolated value, consider to state 'stable'. This is the same study as referenced in EC (2015).

RTR 3-29: Comment acknowledged.

REVIEW 3-30: Soil biodegradation studies by Anderson are also included in list of endpoints EFSA (2008), some figures are the same, but these seem to be best-fit values. I would give preference to 1st order kinetics. Full assessment of the studies can be found in EC (2006; part B.8).

RTR 3-30: Comment acknowledged.

REVIEW 3-31: Section 4. Human and wildlife dietary values. Please specify unit of the LC50, NOEC and MATC (mg/kg bw/d or mg/kg feed).

RTR 3-31: The draft report states that units as reported in each of the studies (Hancock et al. 1994 & 1996 and Toll et al. 1991).

REVIEW 3-31: Information on other bird species is summarised in the risk assessment for birds and mammals carried out by EFSA, see page 99 of EFSA (2008) and EFSA (2014a). Summaries of these studies are available in EC (2006; part B.9).

RTR 3-31: The Method specifies that mallard duck is the only bird species to be included in the toxicity assessment. Other bird species are not considered.

REVIEW 3-32: Section 5. Ecotoxicity data. Literature included in the assessment. Please add information on the search strategy.

RTR 3-32: The method contains details on the literature review process. See TenBrook et al. 2009 Section 3-2.0 and Tables 3.1 and 3.2.

> **REVIEW 3-33:** Some references that were considered as critical in the EU assessments and other
> reviews seem not to be included in the evaluation. Check references in e.g.
> - Appendix B of EFSA (2014b),
> - EC (2015)
> - Smit (2014) and/or Smit et al. (2015; supporting information);
> - Wenzel & Shemotyuk (2014)
> - Morissey et al. (2015; SI),
> - Oekotoxzentrum (2016)
> - Whitfield-Aslund et al. (2017)

RTR 3-33: Many studies test pesticide formulations and therefore cannot be included in the report. The method does not use data from review papers that do not contain original data.

> **REVIEW 3-34:** Please pay particular attention to missing references on mayflies such as Alexander et al. (2007), Roessink et al. (2013) and Van den Brink et al. (2015). I cannot judge if these studies (and other references not yet included) would pass the assessment, but a quality standard derivation for imidacloprid should not be presented without discussing the Roessink-study.

RTR 3-34: The Van de Brink et al. 2015, Alexander et al. 2007, and Roessink et al. 2013 studies were deemed not relevant according to the methodology because they utilized various pesticide formulations rather than technical grade or high purity material.

> **REVIEW 3-35:** It is stated that “No acceptable mesocosm, microcosm or ecosystem (field and laboratory) studies were identified. One microcosm study was available that rated N.” There is no information which studies were retrieved and how they were evaluated. See supplementary information in Sanchez-Bayo et al. (2016), Morissey et al. (2015) and Whitfield-Aslund et al. (2017) for overviews of semi-field tests with imidacloprid, more studies may have been published since then. See also Appendix 2 in Smit (2014) for summaries.

RTR 3-35: Most of the mesocosm studies located during the literature search for imidacloprid used formulations. The draft report has been revised to state that two mesocosm studies that used high purity imidacloprid were identified; one was deemed not relevant/reliable and the other rated highly and was therefore incorporated into the report. Note that mesocosm studies are only used to

compare to the chronic criterion to ensure that the chronic criterion is protective on any effects observed in mesocosm studies.

REVIEW 3-36: Evaluation of aquatic animal data It is appreciated that the evaluation criteria are transparent. However, there is a risk of missing essential information because of the strict way they are applied (scores). I realise that a discussion of the method may be outside the scope of this review.
However, some aspects of the method are of particular interest for the case of imidacloprid. These are:
- The method makes ample reference to guidance of RIVM from 2001. A major update of the method was published already in 2007 (Van Vlaardingen & Verbruggen, 2007), and again revised in 2015 (RIVM, 2015). The current RIVM method is in line with European guidance documents prepared in the context of EU legislation (REACH and Water Framework Directive; see ECHA, 2008; EC, 2018)
- I do not contest the scoring elements that are taken into account in the assessment, because these are important issues for reliability assessment. However, I'd prefer to identify and check those issues that are critical for the test endpoint/substance instead of applying the point-system too rigidly, because not all issues are equally relevant for all studies and compounds. See also Moermond et al. (2016).
- Section 3-2.1.2 of the method (retrieved via https://www.waterboards.ca.gov/centralvalley/water_issues/tmdl/central_valley_
8
projects/central_valley_pesticides/criteria_method/ch_3_final_sept09.pdf) states that "Chronic data expressed as ECx values (from regression analysis), may be used for criteria derivation only if studies are available to show what level of x is appropriate to represent a no-effect level."
It is not clear what type of studies could be used for this purpose. I'm not fully sure, but studies which deliver an EC10 instead of a NOEC seem to be rejected. In recent European guidance preference is given to EC10-values (ECHA, 2008) and EC10 and NOECs are used interchangeably (EC, 2018; ECHA, 2008, 2017; EFSA, 2013).
- Because of the strict scoring system and the focus on NOECs, there is a potential bias towards guideline studies with standard test species. Studies with nonstandard species for which no established guidelines and accompanying reporting criteria exist, are more likely to have reliability points taken off. Because in the scientific literature there is a tendency towards using EC10-values rather than NOECs, results for non-standard species are likely to be presented as EC10. Valuable information may be missed if these studies are not included.
- Section 3-2.1 of the method states the following: "As this methodology is for derivation of criteria specifically for the Sacramento and San Joaquin River watersheds, only use data for freshwater species that are members

of families with reproducing populations in North America will be used for criteria derivation, but all data should be collected as it may be used for supporting information or for derivation of an acute-to-chronic ratio (ACR)." It is not fully clear if reliable endpoints were omitted because of test species belonging to families that are not present in the region. It is noted that in the EU guidance documents, taxonomic diversity of insects is usually considered at the level of Order, which would potentially lead to the inclusion of more species in the dataset.
- Endpoints for non-standard test species are very important for imidacloprid (and other neonicotinoids), because it is demonstrated that other aquatic taxa are much more sensitive to imidacloprid than the standard test species (Sanchez-Bayo et al., 2016). Due to the issues listed above, there is a risk that sensitive non-standard species are not included in the dataset, and even if they are, they are only taken into account for the ACR if there is a valid acute endpoint for the same species. See further comments on the ACR below under 2.7

RTR 3-36: Comments on the method restrictions are acknowledged. Note that the method is limited to species with families represented in North America. A species is included if there is any other species within the taxonomic family is present on the continent, not just within the Sacramento and San Joaquin River watersheds.

REVIEW 3-37: Section 7. Derivation of the acute criterion. The strict evaluation (see above) led to an acute dataset with <5 species, because of which an SSD cannot be performed and the AF-method is used. In my opinion, more valid acute data exist.

In the assessments by EFSA (2014b) and the Dutch evaluations (Smit, 2014; Smit et al., 2015) the lowest accepted EC50 was 0.65 µg/L for Epeorus longimanus from a study by Alexander et al. (2007). However, EFSA (2014b) used an acute SSD, whereas the Dutch acute quality standard is based on a mesocosm, which both resulted in a higher value.
The acute standard derived by Switzerland and Germany is also higher (0.1 µg/L; based on the EC50 for C. seuratti).

RTR 3-37: See RTR 3-34.

REVIEW 3-38: Section 8. Derivation of the chronic criterion
The strict evaluation (see above) leads to a chronic dataset with <5 species, because of which an SSD cannot be performed and the ACR-method is used. The SMACR of Mysidopsis (Americamysis) bahia study should be checked. A SMACR < 1 is highly unlikely for any neonicotinoid, because toxicity increases with time. The MATC values from two tests for growth are reported as 3,806 and 230 µg/L (geomean 935 µg/L), but the

datasheet of the Ward 1991-study gives 3806 and 230 ng/L (→ geomean 935 ng/L → SMACR = 38). If I'm correct, the final multispecies ACR would then be 24.5, and the chronic criterion would become 0.0029 µg/L (2.9 ng/L). The large difference between the two M. bahia tests needs discussion and it is not clear why the lower MATC for reproduction (849 ng/L) is not used to calculate the SMACR.

RTR 3-38: See RTR 3-13.

REVIEW 3-39: The applicability of the generic ACR-method for imidacloprid should be discussed. ACRs in the Dutch assessment varied between 16 and 143, with a geometric mean of 47 which is substantially higher than used in this report. Even higher ACRs are cited by Sanchez-Bayo et al. (2016). These authors point at the fact that the ACR of imidacloprid for insects is highly variable and may span several orders of magnitude. This is due to the fact that the toxicity of imidacloprid is highly dependent on exposure time (Tennekes, 2010; Tennekes & Sanchez-Bayo, 2013).

RTR 3-39: Section 3-4.2 of the method details the ACR procedure, including requirements of both acute and chronic studies that can be used to calculate a SMACR. Within the dataset of the report, there were only a limited number of studies that qualified for the ACR procedure.

REVIEW 3-40: In my opinion, it would be better to rely on chronic data, provided that NOEC/EC10-values for sensitive non-standard test species (e.g., mayflies) are included. In any case, the applicability of an ACR based on standard test species should be discussed (in this section or in section 12), and it should be motivated that the ACR of notoriously insensitive species such as *D. magna* can be used.

RTR 3-40: ACRs are calculated using any relevant and appropriate data, pursuant to the procedure in the method. There is no judgement made on standard versus non-standard species in the method. Objective rating tables are used to determine the quality of the data regardless of the species.

REVIEW 3-41: 9.2, 4th line: imidacloprid is an insecticide, not a herbicide.

RTR 3-41: This has been corrected.

REVIEW 3-42: In my opinion, a major driver to include combination toxicity would be the simultaneous presence of different neonicotinoids in Californian water bodies. The study of Morissey et al. (2015) may be mentioned in this respect. Please note that the cited studies on mixture toxicity do not comprise all neonicotinoids. Please also note that stringent

regulatory measures regarding imidacloprid may induce a shift towards other compounds.

RTR 3-42: Morissey et al. 2015 is a review. The method utilizes original studies only.

REVIEW 3-43: I agree that photolysis should not be taken into account in compliance assessment. The information on the influence of light on toxicity in the laboratory is scattered, and photolysis observed under laboratory conditions is generally not predictive for the field situation.

RTR 3-43: Comment acknowledged.

REVIEW 3-44: 10.1, 5th line. Please mention here that this is a topical test, with mg being the mass of the animal. These tests are not relevant for aquatic quality criteria. This section may change if additional data are included (see comments under 2.4 above).

RTR 3-44: All mosquito studies have been removed from the draft report. While mosquitoes are aquatic during the egg and larval stages of the life cycle, they are airborne/terrestrial at the stage of these topical tests. Therefore, these topical tests are not relevant to the method.

REVIEW 3-45: 10.2 See previous comment. Please indicate why other semi-field studies are not discussed.

RTR 3-45: Most of the mesocosm studies located during the literature search for imidacloprid used formulations. The draft report has been revised to state that two mesocosm studies that used high purity imidacloprid were identified; one was deemed not relevant/reliable and the other rated highly and was therefore incorporated into the report. Note that mesocosm studies are only used to compare to the chronic criterion to ensure that the chronic criterion is protective on any effects observed in mesocosm studies.

REVIEW 3-46: It is agreed that food chain transfer and distribution to other environmental compartments is not relevant for imidacloprid.

RTR 3-46: Comment acknowledged.

REVIEW 3-47: See previous comments on data completeness and the use of the ACR method. Additional data on birds may be found in EFSA (2014a).

RTR 3-47: Comment acknowledged.

3.4. Peer Review 4 – Paul J. Van den Brink, National Aquatic Ecology and Water Quality Management Group, Wageningen University, the Netherlands

REVIEW 4-1: The report does not describe how the ecotoxicity data were collected, how the literature was screened. The acute and chronic data review does not seem to be comprehensive as, for instance, Roessink et al. (2013) and Van den Brink et al. (2016) presents a lot of acute and chronic data points for relevant aquatic species and these have not been reviewed. Roessink et al. (2013) presents 10 acute data points and 7 chronic data points, while Van den Brink et al. (2016) mainly presents acute data for the same species to enable a comparison of sensitivity between generations from different seasons (summer and winter generation). Of the acute data points provided by Roessink et al. (2013) and Van den Brink et al. (2016) only 2 overlap with the acute data points for the species mentioned in Table 3, of the chronic data points only 1 overlaps (Table 7). These data should at least be evaluated for inclusion into the data set. If the data are evaluated as RR, this would increase the number of acute and chronic data points, and, herewith, may affect the criterions.

RTR 4-1: See RTR 2-5.

REVIEW 4-2: Also the data of Sumon et al. (2018) are not evaluated in the report, while they present acute toxicity data for two tropical species, together with the results of a tropical microcosm experiment, and found that tropical species (Cloeon sp. and Diaptomus sp.) and communities may be much more sensitive to imidacloprid compared to temperate ones. The relevance of these findings should be assessed and discussed in the light of the state of California, which is, partly, subtropical.

RTR 4-2: See RTR 2-11. Sumon et al. 2018 utilizes a pesticide formulation.

REVIEW 4-3: The single microcosm study which was evaluated was not accepted. This whilst many more are available, e.g. Alexander et al., 2008; Colombo et al., 2013; Berghahn et al., 2012; Mohr et al., 2012; Hayasaka et al., 2012; Pestana et al., 2009; Kobashi et al., 2017; Rico et al., 2018 and Sumon et al., 2018. It is not clarified why these studies were not included in the evaluation and which one was evaluated as N and why. Some of these studies have already been summarised by Smit et al. (2015).

RTR 4-3: See RTR 2-8 and RTR 3-3.

REVIEW 4-3: Table 8: Lamna should be Lemna

RTR 4-3: This has been corrected.

REVIEW 4-3: Table 9: Reason for exclusion number 4 is not clarified

RTR 4-3: This has been corrected.

REVIEW 4-4: The acute criterion is technically valid, given the studies identified in step 2. Possible inclusion of the data of Roessink et al. (2013) and Van den Brink et al. (2016) will not change the acute criterion as the lowest acute value reported by Roessink et al. (2013) is 1 µg/L which is similar to the lowest value currently present in the data set. Roessink et al. (2013) records an SSD-HC5 based on 96-h EC10 values (HC596h EC10) of 0.084 (0.005–0.422) µg/L, which supports the derived acute criterion of 0.07 µg/L. Smit et al. (2015) states that the water quality standard for short-term concentration peaks can be set at 0.2 µg/L, which also supports the acute criterion. Inclusion of the acute, tropical, toxicity values reported by Sumon et al. (2018) would substantially lower the acute criterion as they report an 96h EC50 of 0.0055 µg/L for Cloeon sp. and of 0.038 µg/L for Diaptomus sp.

RTR 4-4: See RTR 2-11. Sumon et al. 2018 also tests a pesticide formulation.

REVIEW 4-5: The SSD concept is not used due to the absence of acute toxicity data for a warm water fish. Given the relatively insensitivity of fish compared to insects (Morrissey et al., 2015), I would say that an SSD should be constructed based on toxicity data for insect species only. I am not sure whether this is possible after a more thorough screening of the literature for toxicity values for insects.

RTR 4-5: The method requires that a minimal array of highly rated data for specific taxa be used for SSD calculations. Even with additional insect species data, SSD calculations would not be possible under the method.

REVIEW 4-6: The chronic criterion is technically valid, given the studies identified in step 2, although I find the remark in section 8 “Highly rated acute and chronic studies were available only for Daphnia magna” rather strange given the number of studies presented in Tables 3 and 7.

RTR 4-6: The comment in Section 8, “Highly rated acute and chronic studies were available only for Daphnia magna” refers specifically to the availability of both highly rated acute *and* chronic data for any given species.

REVIEW 4-7: Inclusion of the data from Roessink et al. (2013) and other chronic toxicity values present in the literature which have not been included might change the chronic criterion calculation, so a more thorough screening of the literature is recommended.

RTR 4-7: See RTR 2-11. Regarding literature search parameters, see RTR 3-2.

REVIEW 4-8: The lowest 28-d EC10 value presented by Roessink et al. (2013) is 0.024 µg/L, which supports the derived chronic criterion of 0.014 µg/L when no additional AF is needed. Smit et al. (2015) states that the water quality standard for long-term exposure can be set at 0.008 µg/L, which is lower than the chronic criterion of 0.014 µg/L. This is a result of using a relatively low ACR of 9 which is used to calculate the chronic criterion, while Roessink et al. (2013) reports much higher ACR’s between 13 and 336 (geometric mean value of 62).

RTR 4-8: See RTR 4-2.

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