ANSES Opinion
Request No 2019-SA-0202
Related Request No 2018-SA-0113

The Director General

Maisons-Alfort, 17 November 2023

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

on "Updating data on succinate dehydrogenase inhibitor (SDHI)-based plant protection substances"

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It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.
It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).
Its opinions are published on its website. This opinion is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 17 November 2023 shall prevail.

On 6 December 2019, ANSES issued an internal request to update the data from the scientific literature published since SDHI fungicides were approved, in order to determine whether there was any new evidence that might call for an update of its opinion of January 2019 and the report of the associated expert group, and justify a change in the regulatory assessments conducted on the SDHI class of substances at European level (Annex 2).

1. BACKGROUND AND PURPOSE OF THE REQUEST

Following an alert from a group of scientists about the potential risks to human health from the use of succinate dehydrogenase inhibitor (SDHI) fungicides, ANSES issued an internal request on 24 May 2018 to determine whether the scientific information and hypotheses mentioned by these scientists – in light of the data in the literature, European assessments of the substances and data from phytopharmacovigilance – provided evidence demonstrating exposure and risks that had not been taken into account in the assessments of the fungicidal active substances concerned. On 14 January 2019, ANSES published an opinion concluding that the scientific information and hypotheses provided by the aforementioned group of scientists did not provide any evidence supporting a health alert that would justify withdrawing the marketing authorisations for these fungicides (ANSES 2019). However, ANSES called for vigilance at European and international levels and stressed the need for further research on potential toxic effects associated with succinate dehydrogenase inhibition in humans.

On 6 December 2019, ANSES issued a new internal request to update the data from the scientific literature on SDHI substances.

This expert appraisal focused on identifying and characterising hazards by analysing data from the literature and existing toxicity reference values (TRVs) for these substances. This expert appraisal did not include an estimate of the exposures and risks associated with these substances.

A toxicity reference value (TRV) is a toxicological indicator for qualifying or quantifying a risk to human health, in light of the knowledge available. It documents the link between exposure to a toxic substance and occurrence of an adverse health effect. In practice, establishing a TRV involves the following steps, for a given route (ingestion, inhalation, etc.) and type (short, medium or long term) of exposure:

- identifying the target organ(s) and critical effect on the basis of a toxicological profile, with the critical effect corresponding to a duly characterised adverse effect occurring at the lowest dose;
- choosing a study generally showing a dose-response relationship, known as the key study;
- in this study, identifying the highest dose with no toxic effect, known as the critical dose;
- applying uncertainty factors to this critical dose (e.g. to take account of inter-species or inter-individual variability).

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in Expert Appraisals – General requirements of Competence for Expert Appraisals (May 2003)".

The expert appraisal fell within the area of expertise of the following two Expert Committees (CESs): "Plant protection substances and products, biocontrol" (CES Phyto BC) and "Health reference values" (CES VSR). ANSES entrusted the expert appraisal to the SDHI Working Group (SDHI WG), set up in October 2020 following an open call for applications. The

methodological and scientific aspects of the work were presented to the CESs between December 2020 and July 2023.

The results were therefore produced by groups of experts with complementary skills.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts' declarations of interests are made public via the website: https://dpi.sante.gouv.fr/.

In its work, the WG analysed the data and studies taken into account in the regulatory dossiers, conducted a systematic review of the literature and, where necessary, conducted hearings.

The report was validated by the SDHI WG at its meetings of 14, 17 and 18 April 2023. Some experts left the group before the work was completed and are mentioned as contributors up to the dates of their respective resignations, which preceded final validation. During this validation period, some members of the SDHI WG formulated dissenting positions and it was not possible to reach a consensus to resolve them, although this did not prevent the WG from reaching its conclusion. These dissenting positions are set out in the WG's report. The CESs were informed of this prior to formulating their own conclusions.

During the work of the SDHI WG, certain experts submitted additional contributions. Insofar as they contain further information related to the questions in the request, for reasons of transparency, they appear after the annexes to the report. They were made available to the CESs for information, although a lack of time prevented them from being validated by the entire WG, or by the CESs.

A final version of the SDHI WG's report, conclusions and recommendations was submitted to the relevant CESs for validation: on 11 May to the CES VSR and on 6 June to the CES Phyto BC. The CESs' conclusions are set out in Section 3 of this opinion.

In addition, the Agency considered that one of the dissenting positions expressed by two of the WG's experts did not relate to a scientific divergence, but questioned the expert appraisal process itself (Annex 5). After having studied this position, the Agency examined it in light of the fundamental principles of expert appraisal at ANSES[1]. Its analysis is presented in Annex 6 to this opinion.

In view of the SDHI WG's report and conclusions, and the conclusions of the CES Phyto BC and the CES VSR, the Agency formulated its own conclusions and recommendations, which are set out in Section 4 of this opinion.

[1] Fundamental principles and key points of collective expert appraisal at ANSES (November 2012) https://www.anses.fr/fr/system/files/ANSES-Ft-PrincipesExpertise.pdf

3. ANALYSIS AND CONCLUSIONS OF THE WG AND THE CESs

3.1. Analysis and conclusions of the WG

3.1.1. Methodology

The questions put to the SDHI WG were as follows:

- *Should the analysis of available or future information, mainly concerning critical effects and pharmacokinetics, lead to the toxicity reference values for substances being adapted? In this respect, particular attention should be paid to the mitochondrial toxicity of active substances in the SDHI class;*
- *Do the results of vigilance, monitoring or epidemiological studies provide information suggesting a health impact that has not been taken into account in the risk assessment for these substances?*
- *In light of this information, if amendments to the toxicity reference values (TRVs) for SDHI substances are considered necessary, proposals should be made so that they can be presented at European level.*

For plant protection substances, three types of TRV have mainly been defined in the regulatory dossiers:

- the acceptable operator exposure level (AOEL), which sets the acceptable level of exposure for operators, workers, residents and bystanders. This is the maximum amount of active substance (AS) to which these populations can be exposed on a daily basis, without any harmful effect on their health;
- the acceptable daily intake (ADI) is an estimate of the amount of AS in food or drinking water that can be ingested daily over a lifetime without appreciable health risk to the consumer, taking account of all factors known at the time of assessment;
- the acute reference dose (ARfD) is the estimated amount of a substance in food or drinking water, expressed as a function of body weight, that can be ingested over a short period of time, usually during one meal or one day, without appreciable health risk to the consumer, taking account of all factors known at the time of assessment.

To respond to the request, the SDHI WG followed the methodology described in the figure below.

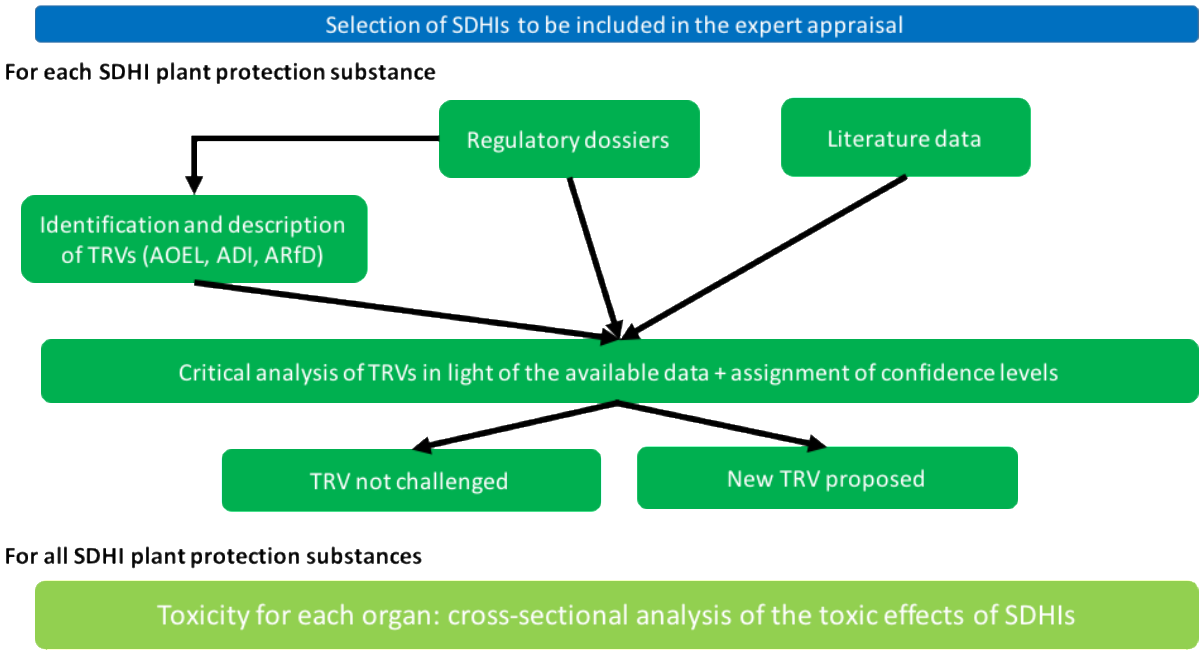


Figure 1: Working method followed by the SDHI WG

The TRVs were described and critically analysed on the basis of regulatory dossiers and a systematic review of the literature, in order to identify whether data relevant to the development of TRVs were available. This expert appraisal did not therefore seek to produce a comprehensive toxicological profile for each of the substances.

The WG analysed the choices made in drawing up these TRVs, focusing on:

- the quality of the key studies
- an analysis of the relevance of the selected critical effects
- the choice of the critical dose

In particular, the WG ensured that the critical doses used as starting points for the TRVs were the most conservative with regard to all the studies relevant to their derivation.

It also assigned confidence levels to the confirmed TRVs or those subject to alternative proposals, applying the ANSES methodological guide (ANSES, 2017).

3.1.2. Selection of SDHI active substances used for plant protection purposes, authorised uses and sales data

The WG reviewed 14 active substances (ASs) from the SDHI class (13 fungicides and 1 acaricide).

These were substances for which a European assessment was available at the time the WG conducted its work. The regulatory statuses and main uses of these SDHIs were identified (Annex 3).

The figure below shows the declared sales figures for plant protection products containing SDHI ASs in France over the period 2008-2020 (data extracted from the national plant

protection product sales database, BNV-D, on 24/06/22). For cyflumetofen, isopyrazam, penflufen and pydiflumetofen, no sales data are recorded in the BNV-D.

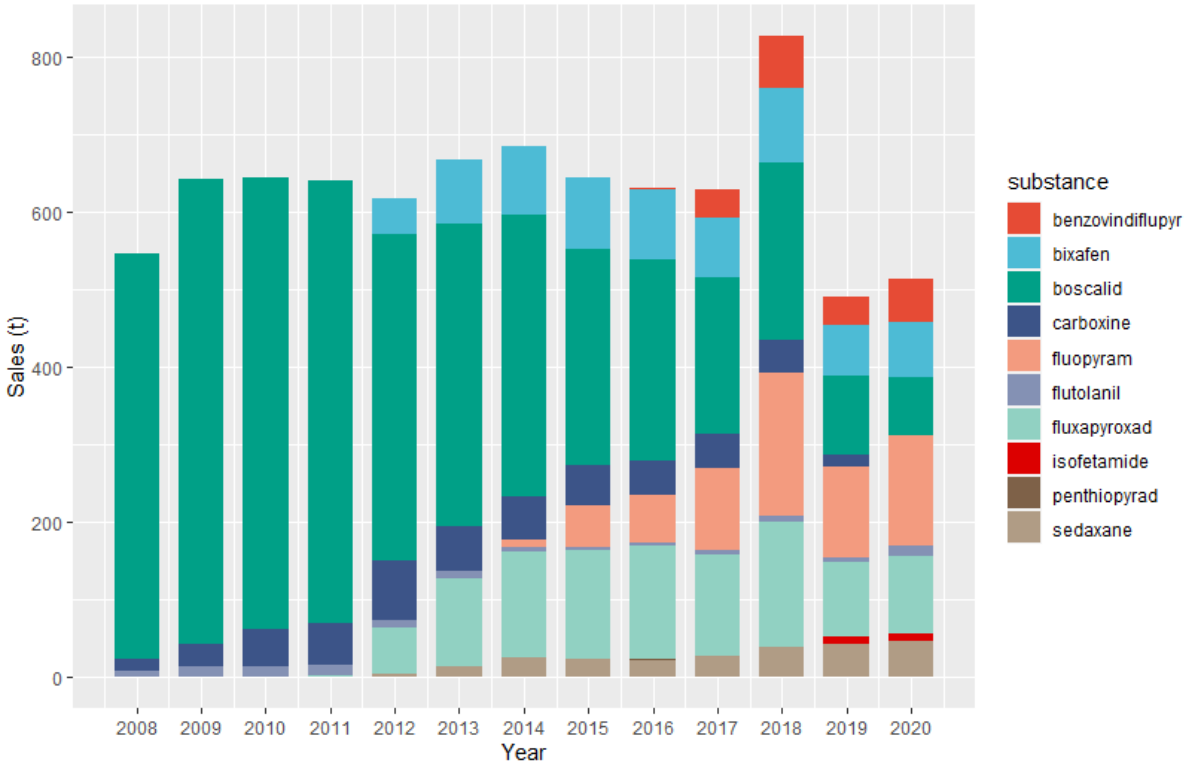


Figure 2: Sales of products containing an AS from the SDHI class in France between 2008 and 2020 (in tonnage of AS and per year of sales)

3.1.3. Biochemistry of succinate dehydrogenase (SDH)

Mitochondria are organelles present in all eukaryotic cells with the exception of red blood cells. They produce energy in the form of adenosine triphosphate (ATP) through the process of oxidative phosphorylation. They therefore play a leading role in the functioning of organs with high energy demands, such as the brain, heart, skeletal muscles, kidneys, liver, etc. Oxidative phosphorylation takes place in the respiratory chain, located in the inner membrane. This metabolic pathway involves five enzyme complexes (complexes I to V) (Figure 3).

This expert appraisal focuses on complex II and the functions of SDH. SDH or mitochondrial complex II catalyses the oxidation of succinate to fumarate. This reaction is part of the oxidative metabolism of carbon substrates.

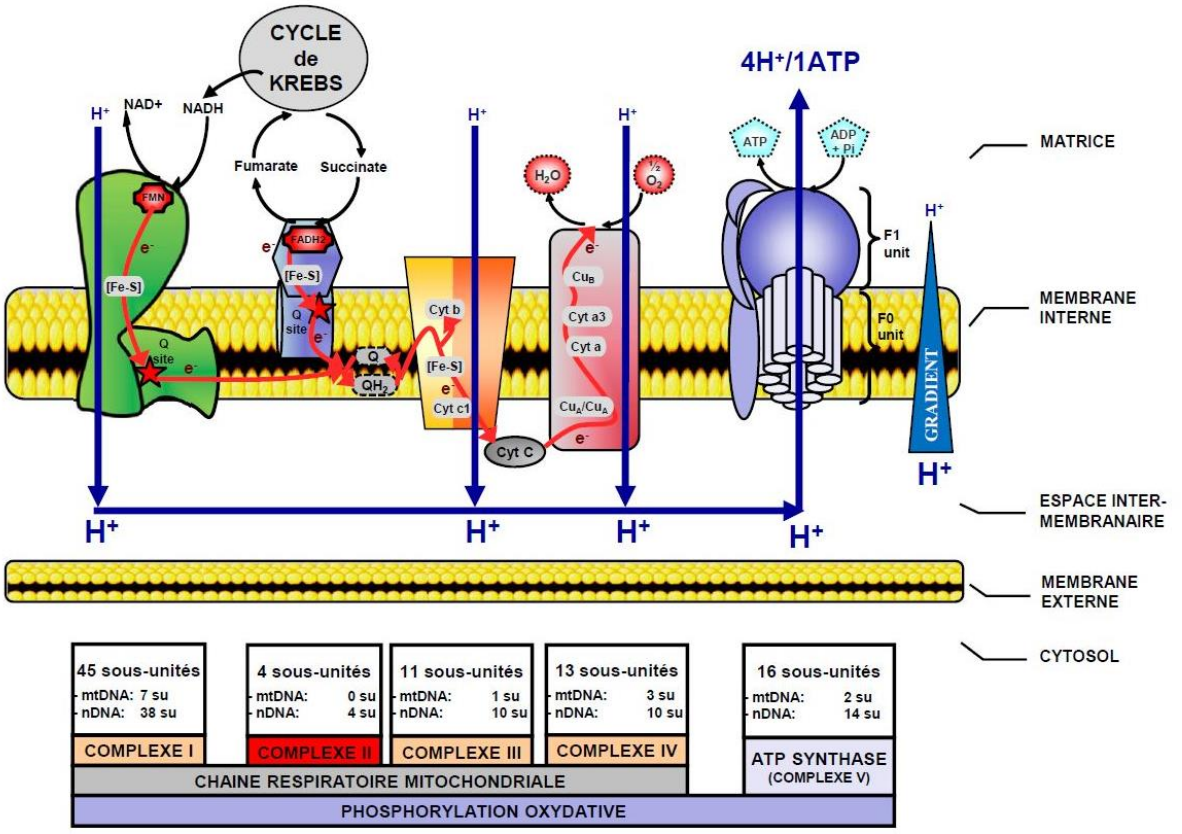


Figure 3: Diagram of the respiratory chain and oxidative phosphorylation in mitochondria, adapted from (Lemarie & Grimm 2011)

There are two mechanisms responsible for SDH dysfunction: mutations in one of the *SDHx* genes and inhibition of the enzyme by xenobiotics.

Regarding inhibition by xenobiotics, the literature mentions two non-pesticide inhibitors: malonate, a competitive inhibitor of succinate, and 3-nitropropionic acid (3-NP), whose inhibition is irreversible. These hydrophilic substances bind to the SDHA subunit. The other inhibitors are larger, more hydrophobic molecules that bind in the ubiquinone pocket, such as 2-thenoyltrifluoroacetone (TTFA) and SDHI pesticides.

3.1.4. Analysis of TRVs resulting from European assessments of active substances

3.1.4.1. Toxicokinetic data

After oral exposure, SDHI ASs are absorbed in proportions ranging from 50 to 95%.

They are rapidly distributed in the body's tissues. Distribution includes both parent substances and their metabolites, as the latter are not differentiated and quantified by these studies. The organs with the highest concentrations of ASs and/or metabolites are generally the liver and kidneys, followed by the gastrointestinal tract.

The amount metabolised can vary depending on the SDHI compound. In general, they are highly metabolised, as shown by the presence of numerous metabolites in urine and faeces. The higher percentages of SDHI in faeces can be explained by the non-absorbed fraction of the parent compound at high concentrations.

More than 80% of the amount administered, monitored by radiolabelling, is eliminated within 48 to 72 hours of exposure, suggesting significant and rapid elimination from the body. The active substance and/or its metabolites are preferentially eliminated in the faeces (between 80 and 90%) and in urine (between 10 and 15%). For some SDHI substances, elimination is dose-dependent, but it is impossible to determine whether this is due to metabolic saturation or to limited elimination caused by tissue retention.

3.1.4.2. Analysis of the TRVs

The literature review did not identify any studies that could be used to derive a TRV. These TRVs are therefore based on the experimental data presented in the regulatory dossiers.

Regarding epidemiological data, Inserm's expert appraisal (2021) found that there were still virtually no epidemiological data on the effects of SDHI ASs on the health of the occupationally-exposed population or the general population. The literature search conducted by the WG did not identify any additional data, particularly data produced after Inserm's collective appraisal.

Of the 39 TRVs available for the 14 substances analysed, the WG proposed amending 11 of them:

- the AOELs for benzovindiflupyr, cyflumetofen and isofetamid;
- the ADIs for carboxin, cyflumetofen, fluopyram, isopyrazam and penthiopyrad;
- the ARfDs for cyflumetofen, penflufen and pydiflumetofen.

The rationales for proposing new values were mainly based on an alternative choice of key study or critical dose (for example, a NOAEL established in the dossier was regarded as a LOAEL by the WG), but also an alternative choice of critical effect or uncertainties related to the quality of the key study. The current TRVs and those proposed by the WG are described in Annex 4 to this opinion.

Among these substances, the WG noted that carboxin and isopyrazam are no longer approved active substances under Regulation (EC) No 1107/2009. In addition, the application for approval of pydiflumetofen is pending at European level.

Dissenting positions were formulated regarding the following TRVs (Annex 5 of the WG report):

- the ADI for bixafen;
- the ARfD for cyflumetofen;
- the ADI for fluopyram;
- the ARfD for penthiopyrad.

3.1.5.SDH dysfunction, diseases and target organs

The WG looked at the effects observed following gene inactivation of SDH or chemical inhibition by non-pesticide inhibitors.

According to the WG, this knowledge can be used to draw analogies between the effects of inactivation by SDH mutation and the effects of chemical inhibition of SDH. This reasoning by analogy is shown in the diagram in Figure 4. However, it cannot be used to extrapolate the effects and diseases associated with SDH inactivation directly to the effects induced by SDHIs, due to several limitations: firstly, the transient inhibition of the enzyme during periods of

exposure to SDHIs, and secondly, the pleiotropic[2] nature of the damage observed with genetic inactivation of SDH.

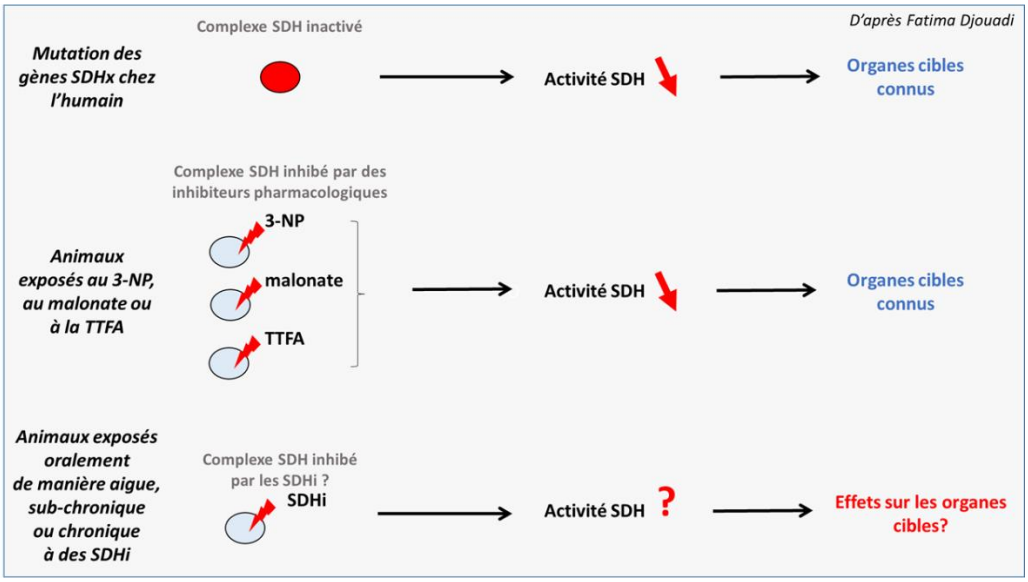


Figure 4: Identification of SDHI target organs by analogy

Pathogenic mutations or variants, which affect the *SDHx* genes and cause inhibition of complex II, can give rise to:

- either a primary deficiency of complex II, i.e. a hereditary deficiency with germline mutations passed on to the offspring. This concerns rare diseases belonging to the large family of mitochondrial diseases, mainly affecting muscles, including the heart and central nervous system;

- or a susceptibility to certain types of cancer that develop when a heterozygous inherited mutation in one of the *SDHx* genes is associated with a mutation or deletion in the second somatic allele.

On this basis, the WG put forward the hypothesis of a particular sensitivity to SDHIs in subjects with a mutation in the heterozygous state. These mutations destabilise the proteins, generally leading to a reduction in SDH enzyme activity, which varies from one individual to another. The relationship between the degree of enzyme inactivation and the degree of inhibition of mitochondrial respiration is unknown. Heterozygous individuals have both a mutated form of the SDH enzyme complex and a normal form, resulting in reduced SDH activity. In these subjects, the impaired residual SDH activity may be exacerbated by SDHI inhibition. As in individuals with a homozygous mutation, this could lead to an accumulation of succinate, a major event in establishing the tumour phenotype.

The WG also investigated the neurological effects associated with exposure to non-pesticide SDHIs. Generally speaking, all the experimental data on 3-NP and malonate show that the striatum is particularly vulnerable, with motor symptoms that appear to be at least partially linked to inhibition of SDH activity. However, the neurotoxicity does not have absolute striatal specificity. TTFA, which is closer to SDHI pesticides than 3-NP and malonate in terms of its

[2] The ability of a gene to determine several traits

molecular target in the mitochondrial chain, induces damage to the dopaminergic nervous system in mice.

3.1.6.Toxicity for each organ

The internal request stated that "*particular attention should be paid to the mitochondrial toxicity of active substances in the SDHI class*". The WG therefore carried out a cross-sectional analysis of the toxic effects common to several SDHIs studied with regard to mitochondrial toxicity, to enable a comparison of their toxicity by organ or by system.

Regarding the liver, the experimental studies analysed in the regulatory dossiers indicated that exposure to most SDHIs induced liver effects. These were mainly characterised by hypertrophy of the hepatocytes with increased liver enzyme activity. This liver damage was often accompanied by thyroid effects. In particular, for 11 SDHIs (benzovindiflupyr, bixafen, boscalid, fluopyram, fluxapyroxad, isofetamid, isopyrazam, penflufen, penthiopyrad, pydiflumetofen and sedaxane), liver damage was selected as the critical effect for setting the TRV (AOEL or ADI). Several SDHIs induced liver tumours at doses higher than those used to establish the TRVs. According to the regulatory dossiers reviewed by the WG, induction of metabolising enzymes in the liver following exposure to SDHIs is based on the activation of receptors, particularly CAR (constitutive androstane receptor) / PXR (pregnane X receptor).

A dissenting position was formulated on this part (see Annex 5 of the WG report).

Regarding thyroid toxicity, the experimental studies analysed in the regulatory dossiers indicated that exposure to most SDHIs induced thyroid effects. Various thyroid effects were found in isolation or in combination: increased relative weight of the gland, hypertrophy and/or hyperplasia, altered colloid, etc. For seven SDHIs (benzovindiflupyr, bixafen, boscalid, fluopyram, flutolanil, penflufen and sedaxane), thyroid effects was selected as the critical effect in development of the TRV (AOEL or ADI). In the regulatory dossiers, a mechanism of action via activation of the CAR nuclear receptor was generally put forward to justify the non-relevance of thyroid effects in humans. However, the WG considers that this conclusion is open to debate due to experimental shortcomings or inconsistent results, as well as the presence of thyroid gland effects observed in dogs, whose regulation of thyroid function is similar to that of humans. This information warrants further investigation. In humans, therefore, uncertainties remain about the potential disruption of thyroid regulation.

A dissenting position was formulated on this part (see Annex 5 of the WG report).

Regarding the adrenal glands, effects (histological and/or relating to weight) were observed for the majority of SDHIs analysed by the WG. In particular, statistically significant impairment and/or impairment observed in most of the animals tested where the statistical result was not specified in the regulatory dossier (such as cortical and/or glomerular hypertrophies, cortical vacuolation) was reported for benzovindiflupyr, cyflumetofen, fluopyram, fluxapyroxad, isofetamid and penthiopyrad. With the exception of cyflumetofen, these effects appeared at doses higher than those used to develop the TRVs. Nevertheless, for these compounds, the WG concluded that adrenal toxicity should be carefully considered through the prism of their modes of action. In this sense, although this effect appears to be a non-significant event, the

development of pheochromocytomas observed in response to bixafen and flutolanil exposure was seen by the WG as a warning signal, due to the mechanism of action of SDHIs and the susceptibility conferred by SDH inactivation on the development of this type of neuroendocrine tumour in humans.

Regarding the visual system, SDH mutations affect eye development. Recent articles have described adverse effects on the eye associated with exposure to certain SDHIs (bixafen, boscalid, fluxapyroxad, isopyrazam and sedaxane) in non-mammalian species. Consequently, the WG was particularly interested in the ocular observations reported in the regulatory studies, even when these were not statistically significant. For example, damage, particularly to the retina, was observed for several SDHIs. This damage was statistically significant for isopyrazam (at exposure doses higher than those used to establish the current TRVs) and was observed occasionally without statistical significance for other compounds (bixafen, cyflumetofen, fluopyram and penthiopyrad). Most of the damage was reported in prenatal developmental toxicity studies and mainly concerned microphthalmia and retinal folds. Occasional damage was also seen in adulthood (paleness of the back of the eye, retinal atrophy or lens degeneration), suggesting lifelong sensitivity of the visual system. This is a signal that should be further investigated, particularly regarding eyeball size, along with a developmental neurotoxicity study to clarify the relevance of this damage.

Regarding the nervous system, the neurological effects of SDHIs described in the regulatory dossiers were examined in light of what is known about the effects of non-pesticide SDHIs (3-NP, malonate and TTFA). These substances have been shown to have an adverse effect on the striatum and/or substantia nigra in rodents and primates, associated with their mode of action targeting mitochondrial complex II. The regulatory dossiers on SDHIs reported neurological behavioural or motor disorders, which were usually transient and occurred during short exposure periods. In particular, determination of ARfDs was based on critical effects reported in acute neurotoxicity studies in rats for four SDHIs (benzovindiflupyr, fluopyram, penflufen and sedaxane). Neurological symptoms were also observed with other SDHIs, but at higher doses than those used to determine the TRVs. The WG noted that the subchronic and chronic exposure studies in mice and rats did not include thorough tests for possible chronic neurotoxicity. This would require not only a search for behavioural and motor deficits, but also specific neuropathological investigations. These should be able to identify any damage to the dopaminergic nervous system, which is targeted by several chemicals that inhibit SDH.

Regarding the kidneys, regulatory studies carried out with benzovindiflupyr, boscalid, carboxin, the B-3 metabolite of cyflumetofen, fluopyram, flutolanil, isofetamid and penthiopyrad indicated varying degrees of kidney damage. With the exception of carboxin, for which the current AOEL is based on kidney effects, these effects were not considered relevant for humans in the regulatory dossiers, on the basis of the observation of an accumulation of α2u-globulin in male rats. Nevertheless, the WG took these effects into account when proposing the ADI for penthiopyrad. Moreover, the WG noted that certain effects have been observed in other species (mice and, in the case of carboxin, dogs) and in both sexes.

Regarding the reproductive organs, reproduction and development, certain effects were observed at the doses used to establish the TRVs: reduced sperm motility exclusively for benzovindiflupyr, reduced foetal weight for bixafen and penthiopyrad, implantation losses and foetal resorptions for flutolanil and fluxapyroxad, skeletal variations for isofetamid and pydiflumetofen. The adverse effects on reproduction and development, when they occurred, were variable depending on the SDHIs and it was not possible to identify one or more common effects. In the case of isopyrazam, delayed ossification and eye malformations were the rationale for its developmental toxicity classification in category 1B. Pydiflumetofen is classified as a category 2 reproductive toxicant on the basis of the delayed puberty observed in the two-generation study.

Regarding cardiac development, this does not clearly appear to be a target of SDHIs at the doses used to develop the TRVs. Cardiac malformations were only reported in the regulatory dossier for isopyrazam at doses higher than those used as the basis for the TRVs. Nevertheless, cardiac toxicity has been reported in the literature in zebrafish embryos with bixafen, carboxin, flutolanil and fluxapyroxad. On this basis, the WG stressed the need to pay greater attention to examining the heart in regulatory analyses.

Regarding the endocrine system, assessment of endocrine disruption must comply with the methodology in the ECHA/EFSA guidance document in the context of the regulations on plant protection substances (Regulation (EC) No 1107/2009) (ECHA, EFSA and JRC et al. 2018). However, the dossiers reviewed pre-date the implementation of this guidance document and did not therefore sufficiently investigate the endocrine-disrupting potential of SDHIs. During the WG's review of the regulatory documents, the dossiers for certain substances showed effects that could potentially be explained by an endocrine-disrupting mechanism. The WG therefore stressed that when these substances are re-assessed, particular attention will have to be paid to their ED potential, with regard to the effects observed by the WG, especially on the thyroid and adrenal glands.

3.1.7. Conclusions of the WG

The SDHI WG included in its expert appraisal the SDHI active substances used for plant protection purposes for which a European assessment was available at the time it conducted its work, i.e. 14 SDHI ASs.

As provided for in the request, the SDHI WG began by examining the TRVs currently in force (AOEL, ADI, ARfD) in order to make proposals for amendments if necessary. To do this, it conducted an analysis based on the regulatory dossiers for the 14 SDHI substances, and more specifically on the summary of the rapporteur Member State's assessment (Volume 1) and toxicology and metabolism data (Volume 3B6), as well as the EFSA conclusions and the RAC[3]. opinions Where necessary, the experts were given access to detailed study reports. At the same time, a bibliographical search of the scientific data available in the academic literature was undertaken in order to identify the adverse effects of SDHIs and the underlying mechanisms of toxicity. It should be remembered that the WG report was not intended to produce an exhaustive toxicological profile for each of the substances.

[3] Risk Assessment Committee of the European Chemicals Agency (ECHA)

Analysis of the 39 TRVs examined for the 14 compounds in the SDHI class led the WG to propose amendments to 11 of them: three AOELs, three ARfDs (2 values challenged and 1 new value proposed) and five ADIs. These amendments were prompted by the reclassification of NOAELs as LOAELs, the selection of key studies deemed more relevant, or the inclusion of an additional uncertainty factor. These amendments led to these TRVs being reduced by factors of between 1.5 and 3.3.

The WG noted that a number of SDHIs act on the same organs, such as the central and peripheral nervous systems (including the eyes), kidneys, thyroid, adrenal glands and liver. In particular, the WG noted similarities between the effects induced by gene inactivation of SDH in humans and the adrenal gland toxicity caused by SDHIs. The WG also observed that studies of the link between exposure to SDHIs and SDH inhibition are not a regulatory requirement and are therefore not included in the industrial dossiers. The literature review did not provide any answers on this point. The WG stressed the importance of developing specific adverse outcome pathways (AOPs) resulting from a mitochondrial complex II deficiency (see RECO4).

The WG's review of the TRVs found uncertainties related to the generally moderate or even low confidence levels assigned to these values. Additional analyses would make it possible to better characterise potential hazards and confirm/amend the TRVs, thereby reducing these uncertainties (see RECO1).

The toxicokinetic studies on the SDHIs in the regulatory dossiers, carried out with radiolabelling, are unable to differentiate the parent compounds from the metabolite(s) of interest, and cannot therefore be used to estimate distribution to the different organs. This means that generic physiologically-based pharmacokinetic (PBPK) models cannot be produced (see RECO3).

Moreover, the WG considers that the current assessment of SDHIs alone is incomplete. A hazard assessment should be conducted for formulations containing active substances that have an effect on the respiratory chain and could potentially influence the observed effects.

The WG noted major shortcomings in certain regulatory dossiers. It feels that additional tests are necessary on nephrotoxicity or neurotoxicity, including during development, because of warning signs (see Chapter 8 of the WG's report: Organ toxicity). Certain experimental studies with high mortality rates were taken into account in the regulatory assessments when they should have been rejected and therefore repeated. The WG also regretted the inappropriate use of historical controls to reject statistically significant effects. Furthermore, the dossiers examined did not investigate endocrine-disrupting potential, as their assessments were prior to implementation of the 2018 guidance document. These shortcomings could be rectified during the renewal assessment of these substances.

In addition, the WG feels that the tests required when assessing the regulatory dossiers for these substances are both inappropriate and inadequate for assessing the specific toxicity of SDHIs, based on the data in the literature. This led the WG to make specific recommendations on the need to implement a testing strategy for assessing mitotoxicity and adapt certain OECD guidelines (see RECO1).

Regarding the epidemiological data, Inserm's 2021 expert appraisal found that there were still virtually no epidemiological data on the effects of SDHI active substances on the health of occupationally-exposed populations or the general population. The literature search conducted by the WG did not identify any additional data. The WG draws attention to the possible vulnerability of populations with a dysfunctional respiratory chain (around 1 in 4000 people in France) in the event of exposure to SDHIs, particularly occupational exposure.

Lastly, although the request only concerned the hazards, the WG emphasised the lack of data on population exposure and biomonitoring, which could complicate assessment of the health risks (see RECO2). The WG also recommends that an expert appraisal be conducted on the impact of SDHIs on biodiversity and ecosystem health (see RECO5).

3.1.8.Recommendations of the WG

Based on the detailed information in its report, the WG makes the following recommendations:

Implement an integrated approach to the assessment of mitotoxicity in general and complex II inhibition in particular, as part of a regulatory assessment for chemicals (RECO1)

The WG recommends developing a sequential strategy to assess mitotoxic potential (RECO1A1 and RECO1A2, RECO1C) and its functional consequences (RECO1B), using a battery of *in vitro* and *in vivo* tests based on what has been done by the US EPA (Hallinger *et al*. 2020).

The WG recommends an initial assessment of mitotoxicity (RECO1A) by carrying out:

- three tests to assess oxidative phosphorylation function (RECO1A1);
- additional *in vitro* tests (RECO1A2) if oxidative phosphorylation is impaired;
- in the case of mitotoxicity that is unrelated to complex II inhibition, the WG recommends developing specific additional tests.

If the tests proposed in RECO1A (RECO1A1 and RECO1A2) identify complex II inhibition, the WG recommends:

- conducting appropriate functional and analytical tests in relevant *in vivo* vertebrate models, in order to assess the effects on tissues and organs, in particular those identified as sensitive in the WG's report (Chapter 8 of the WG report, available as a supplement to this opinion), or in the literature (RECO1B);
- following these *in vivo* tests, conducting enzyme tests to assess the activity of complex II (SQR/SDH) in the tissues and organs concerned by RECO1B (RECO1C).

Improve knowledge of population exposure levels to SDHIs (RECO2)

The WG recommends:

- including SDHIs in national biomonitoring programmes;
- including SDHIs among the substances screened for in total diet studies (TDSs), including those on infant diets, and coupling this information with the French individual food consumption studies (INCA);
- supporting epidemiological research aimed at identifying the health effects of SDHIs, in the general population or in occupationally exposed populations, based on objective exposure measurements.

Improve pharmacokinetic studies in general for a better use of *in vitro* toxicological data (RECO3)

The WG therefore recommends that toxicokinetic studies include quantification of the compounds of interest to enable the parent substances to be differentiated from their metabolites in the various tissues. The WG also recommends:

- using PBPK modelling to take account of absorption, distribution, metabolism and elimination (ADME) physiological processes, determine internal exposure from external exposure and estimate *in vivo* concentrations from effective *in vitro* concentrations;
- using the same aqueous formulations to solubilise SDHI substances for both toxicokinetic studies and repeated toxicity gavage studies;
- conducting an intravenous study in parallel with the single-dose oral toxicokinetic study.

Encourage the development of adverse outcome pathways (AOPs) (RECO4)

In order to structure the information available to date and guide integrated test strategies (ITSs) that are relevant and suited to the toxicity profile of SDHIs, the WG recommends:

- developing an AOP for "SDH inactivation and carcinogenesis";
- developing an AOP for "SDH inhibition and neurotoxicity", including neurodevelopment and neurodegeneration.

Assess the effects of SDHIs on ecosystems and their impact on biodiversity (RECO5)

The WG recommends conducting a collective expert appraisal specifically devoted to the effects of SDHIs and the assessment of risks to biodiversity and ecosystem health.

3.2. Analysis and conclusions of the CESs

3.2.1.CES on "Plant protection substances and products, biocontrol"

The SDHI WG's report was validated by the CES on "Plant protection substances and products, biocontrol". Regarding the chapter entitled "SDH dysfunction, diseases and target organs" (Chapter 7 of the WG report), a majority of experts abstained. The experts who abstained considered that it was not possible to draw analogies between the effects of a permanent inactivation by SDH mutation and the effects of chemical SDH inhibition of unknown intensity and duration. Moreover, the chemical inhibitors cited in the report, such as 3-NP, are of a different nature to SDHIs, meaning that it cannot necessarily be assumed that their mechanisms of action are similar.

3.2.2.CES on "Health reference values" (CES VSR)

This opinion aims to explain the CES VSR's partial validation of the report prepared by the SDHI WG. The CES VSR works together with the WGs reporting to it, in accordance with ANSES procedures. Regardless of the chemical agent or substance studied, after reading the WG's report, the CES may, where appropriate, ask for clarification and/or suggest modifications when the CES experts believe this is justified in light of the available scientific data. The WG then takes into account the CES's proposals when drawing up the final version of the report.

After taking account of the comments made by the CES VSR, the SDHI WG drew up the final version of its report. As this document could then no longer be modified, the CES VSR, after reading it, decided not to endorse it in its entirety and to validate only certain parts of the report for the reasons described below.

Chapters 1 to 5[4] were validated by the CES VSR. However, it noted that the use of the "skull and crossbones" icon in Chapter 3's Figure 14, suggesting a lethal toxicological effect for exposed individuals, was inappropriate. Figure 11 in the 2023 article by F. Bouillaud[5] *(a member of the SDHI WG)*, describing the supposed effects of different levels of SDHI inhibition, would have been more appropriate, as it directly indicates that cell death can occur if the compensatory effect is exceeded.

Regarding Chapter 6 on the TRVs, the CES VSR validated all the values selected or established by the SDHI WG. However, it did not validate certain parts of the text in this chapter.

1) Regarding the "points of concern[6]":

- Overall, the CES VSR did not validate the points of concern included in this chapter. Chapter 6 **focuses on the choice or establishment of TRVs**:
    - either the available data are sufficient to challenge the choice of critical effect, key study or critical dose (unsuitable dose range, etc.), in which case this should be included in the critical analysis of the TRV and taken into account, for example via an uncertainty factor;
    - or the scientific data do not provide sufficient evidence for such a challenge to the TRVs, and these "points of concern" have no place in this chapter.
- Moreover, most of the "points of concern" were based on isolated or sporadic observations, with no statistically significant excess risk or dose-response relationship, and no evidence to support their reproducibility. According to internationally accepted criteria, these observations cannot therefore be described as "effects" of exposure to the tested agent (WHO, 2004[7]). If the mechanistic evidence is sufficient to constitute a set of arguments justifying specific recommendations for further studies, it should be discussed in Chapter 8.
- Lastly, some "points of concern" relate to effects (in line with the criteria mentioned above) for which the available data prove that they occur at doses higher than the TRVs selected or developed by the WG. As no robust scientific argument has been provided to support the possibility that these effects could occur at lower doses, this is a normal observation when establishing TRVs[8] and does not justify a specific "point of concern".

2) Regarding boscalid, although the value was validated, the CES VSR considers the argument on the AOEL to be superfluous (see Chapter 6.3.2.1.2), and points out that its wording could cast doubt on the dataset, which is not justified by the available experimental data. The WG did not challenge the existing TRV and did not propose including any additional uncertainty factors, particularly related to the dataset.

[4] Chapter 1: Context, Chapter 2: Methodology, Chapter 3: Selection of SDHI active substances, authorized uses and sales data, Chapter 4: SDH biochemistry, Chapter 5: Previous assessments
[5] Bouillaud, F. Inhibition of Succinate Dehydrogenase by Pesticides (SDHIs) and Energy Metabolism. *Int. J. Mol. Sci.* **2023**, *24*, 4045 https://doi.org/10.3390/ijms24044045
[6] Points of concern were defined by the WG as points that do not have an impact on the TRVs but help to identify concerns that may relate to critical effects or the quality of available data
[7] WHO-IPCS 2004: IPCS Risk Assessment Terminology. Part 1: IPCS/OECD Key Generic Terms used in Chemical Hazard/Risk Assessment. Part 2: IPCS Glossary of Key Exposure Assessment Terminology
[8] This is because TRVs are developed taking into account the adverse effects that occur at the lowest doses

3) The CES VSR acknowledges that the use of historical controls varies from one study to another, and in fact validated the ADI for carboxin and the ARfD for pydiflumetofen (situations where historical controls led to the identification of a NOAEL rather than a LOAEL). However, the CES VSR noted a lack of consistency in how the SDHI WG used the historical controls: challenging these controls when they contributed to an observation not being selected as an effect (boscalid, isopyrazam), but on the contrary using them as a supporting argument when an observation appeared to be more frequent than in the historical controls (carboxin (carcinogenic effect), penflufen, penthiopyrad).

Regarding Chapter 7, the CES VSR wishes to highlight the considerable amount of work and the abundance of descriptive data on mitochondrial diseases that it contains.

From a scientific perspective, the CES VSR considers that:

- the WG's report put forward the hypothesis that all the reported effects of SDHIs can be explained by their inhibitory effect on SDH, without providing any scientific proof of this;
- the intensity and duration of SDH inhibition induced by SDHIs, which is the subject of the report, was not sufficiently taken into account. Indeed, while the report clearly sets out the effects of a permanent or long-term deficiency of genetic origin or induced by certain non-pesticide SDHIs, it does not provide any evidence that the partial and transient inhibition of SDH, as can reasonably be expected from the use of pesticides whose active substance is an SDHI, could cause the same effects;
- certain comparisons – concluding, for example, that there is a common mechanism between certain diseases of an uncertain physiopathological mechanism and certain chemical agents used experimentally – are insufficiently substantiated. This is the case, for example, with Huntington's disease and exposure to 3-NP.

The CES VSR regrets that this chapter does not simply conclude with a summary listing the questions to which the WG experts expected answers from the literature concerning the health impact of partial and transient inhibition of SDH. It therefore did not validate this chapter.

Regarding Chapter 8, the principle of cross-reading the data from the literature to identify possible common effects of SDHIs on certain organs, without being totally innovative, is original. The CES VSR is open to any methodological developments likely to simplify the assessment of chemical classes and/or mixtures, and therefore examined it closely.

Nevertheless, the CES VSR feels that the exercise was not as productive as expected, for two main reasons:

- firstly, several sub-chapters included as "effects" isolated observations that were not statistically significant, with no dose-response relationship (the paragraph on ocular effects is a good illustration of this). While the CES VSR accepts that non-monotonic dose-response relationships may exist, the statistical significance of variations in response is still essential to qualify them as "effects", even more so if there is no experimental reproducibility in the available literature. The CES VSR therefore disputes that such observations could be considered as effects, which reduces the relevance of a number of sections in this chapter;
- as this is a report whose purpose is to define TRVs, the CES VSR expected this chapter to provide scientific arguments, backed up by literature data, suggesting that:
    - certain effects likely to be induced by SDHIs have not been examined (or have been insufficiently examined) in the available studies;

- or that certain effects already observed in the available studies could potentially occur at doses lower than those tested in these studies.

In both cases, this chapter would have been an opportunity to issue recommendations for additional studies to explore these assumptions and serve as a new reference, if appropriate, for developing TRVs (new key study, new critical effect and/or new critical dose). This purpose, for which the summary boxes at the end of certain sub-chapters are ideally suited, seems to have been forgotten in the description of several potential SDHI target organs. Chapter 8 as written seeks to demonstrate that SDHIs are harmful to all these organs (even though some of the "effects" identified by the WG were not statistically significant), without in the end providing any convincing argument that would challenge the critical effects used to develop the TRVs, or the critical doses used to formulate them. Interpreting a "sum" of statistically insignificant observations in light of an unverified assumption based on the available literature does not contribute to the establishment of TRVs, which is the main purpose of this report. The CES VSR therefore did not validate this chapter. It points out that the method for establishing a TRV is based on the identification of a critical effect (one whose incidence is significantly increased by exposure and which occurs at the lowest dose). Consequently, as the TRV is based on the effect occurring at the lowest dose, it protects against all effects, which are therefore all taken into account.

If Chapters 7 and 8 are read in succession, it gives the impression that biological plausibility is the *primum movens* of the assertion of an effect, making its experimental, clinical or epidemiological confirmation secondary. While the existence of a possible mechanism of action may be sufficient to make assumptions and prompt experimental studies to confirm it, or even to identify the resulting health effects, the development of a TRV is above all supported by the existence of a critical effect and critical dose based on a statistically significant increase in the occurrence of this effect. The existence of a mechanism of action that could explain the effect whose incidence is significantly increased is an argument to support the causal nature of the association between exposure and effect. In view of the level of evidence required to establish a TRV, it cannot be developed on the basis of a "theoretically plausible adverse effect" according to the wording proposed on page 178 of the report.

The CES VSR therefore regrets that the considerable amount of work produced by the WG was not essentially devoted to a critical analysis of the current TRVs, with a view to their revision or establishment, as these are measures that would guarantee the safety of exposed populations. Chapter 7 demonstrated the importance of the mitochondrial system in general, and the SDH complex in particular, and the seriousness of long-term damage. However, the CES VSR expected it to be used to draw up a list of questions likely to arise regarding the action and, above all, the possible health effects of SDHI pesticides. This would have identified the points to which the body of data does not provide an answer, and substantiated recommendations for targeted additional studies. While not written with this in mind, this chapter seems to suggest that insofar as mitochondria are ubiquitous, any observation (whether or not it is statistically significant) can be attributed to SDH inhibition.

Regarding the WG's recommendations, the CES VSR does not support a number of the research recommendations made. While the CES VSR does in principle favour conducting studies to better identify the effects, understand the mechanisms of action and measure the impact of exposure to SDHIs, some of the recommendations made by the WG:

- do not seem to be sufficiently well-argued or justified by the available data,
- do not seem to justify challenging the TRVs or developing new ones.

More specifically:

- Recommendation 4 "Encourage the development of adverse outcome pathways (AOPs)" proposes that AOPs be developed. Although it would obviously be beneficial to structure the available mechanistic data whenever an adverse outcome is confirmed experimentally, or even epidemiologically, the data available at this stage do not suggest that this could challenge the existing TRVs;
- regarding Recommendation 5 "Assess the effects of SDHIs on ecosystems and their impact on biodiversity": because its implementation would not challenge or improve the existing TRVs relating to the effects of human exposure, the CES VSR did not validate this recommendation as it falls outside the scope of its expertise.

Regarding the "personal contributions", the CES VSR notes their unusual nature: they are not the result of collective work and validation. The CES VSR considers that these contributions equate to hearings and should not therefore form part of the collective expert appraisal report. Accordingly, the CES VSR does not issue any opinion on these "contributions", which are only binding on their author(s).

The CES VSR wishes to point out that its role is to select or develop TRVs in collaboration with the WGs reporting to it, and not to issue an opinion on the relevance of using a substance or placing it on the market. Reference values can only be established on the basis of robust scientific data and proven health effects for which there is sufficient evidence of a causal link with exposure to the substance in question. The CES VSR therefore issued this opinion with this objective in mind, in accordance with its scientific methodology and on the basis of the data currently available. The TRVs for SDHIs, like all TRVs, will need to be reassessed if new experimental or epidemiological data reveal one or more new health effects (according to the criteria reiterated several times in this opinion) and/or occurring at lower exposure doses than those used to draw up the current TRVs.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

Following an alert from a group of scientists about the potential risks to human health from the use of succinate dehydrogenase inhibitor (SDHI) fungicides, ANSES issued an internal request on 24 May 2018 to determine whether the information and hypotheses mentioned by these scientists – in light of the data in the literature, European assessments of the substances and data from phytopharmacovigilance – provided evidence demonstrating exposure and risks that had not been taken into account in the assessments of the fungicidal active substances concerned. On 14 January 2019, ANSES published an opinion concluding that the scientific information and hypotheses provided by the aforementioned group of scientists did not provide any evidence supporting a health alert that would justify withdrawing the marketing authorisations for these fungicides. However, ANSES called for vigilance at European and international levels and stressed the need to step up research on potential toxic effects in humans.

Among the actions taken to address this alert, the Agency contacted European and international bodies (EFSA, ECHA, European Commission, US EPA, PMRA[9]) mainly in order to inform them and find out whether they were aware of similar concerns regarding SDHIs. It then requested Inserm's analysis as part of the Institute's finalisation of its collective expert appraisal on Pesticides and Health, to ensure that the question of the links between exposure and the health effects of SDHIs was adequately updated in light of the latest available data. Lastly, given the lack of relevant epidemiological data, ANSES launched a feasibility study – as part of its phytopharmacovigilance mission – prior to conducting specific epidemiological research.

As part of the ongoing response to this alert, ANSES issued two complementary internal requests, based mainly on the recommendations made during the first expert appraisal. One of the requests concerns an assessment of cumulative exposure to active substances in the SDHI class, which is addressed by a supplementary opinion to this one.

In addition, on 6 December 2019, ANSES issued an internal request to update the data from the scientific literature published since the active substances in the SDHI class were approved, in order to determine whether there was any new evidence that might call for an update of the January 2019 opinion and report of the collective expert group, and justify a change in the assessments of the SDHI class of substances conducted in the European regulatory context. This is the purpose of this opinion, which supplements the one on cumulative exposure that has also been published.

As part of this internal request, the following questions were asked:

- *Should the analysis of available or future information[10], mainly concerning critical effects and pharmacokinetics, lead to the toxicity reference values for substances being adapted? In this respect, particular attention should be paid to the mitochondrial toxicity of active substances in the SDHI class;*

[9] Health Canada's Pest Management Regulatory Agency
[10] Inserm's collective expert appraisal in particular

- *Do the results of vigilance, monitoring or epidemiological studies provide information suggesting a health impact that has not been taken into account in the risk assessment for these substances?*
- *In light of this information, if amendments to the toxicity reference values (TRVs) for SDHI substances are considered necessary, proposals should be made so that they can be presented at European level.*

In particular, ANSES expected this expert appraisal to apply a cross-cutting approach that took account of all SDHI ASs, based on an analysis of the evidence available in the literature and in the regulatory dossiers, to enable the WG to formulate proposals regarding the toxicity reference values.

A toxicity (or health) reference value (TRV) is a toxicological indicator used to qualify or quantify a risk to human health for a given route of exposure and a given timescale (short, medium or long term), in light of the available knowledge. In this sense, a TRV expresses the state of scientific knowledge in order to ensure the protection of people exposed to a hazard. The critical effect then refers to the effect occurring at the lowest levels of exposure, which is sufficiently scientifically documented. Therefore, the major challenge in relation to the questions about the SDHI alert is not only to determine whether a mitochondrial toxicity mechanism leads to an adverse effect, but above all to identify whether this toxicity manifests itself at a lower level of exposure than the one defined by the TRV.

To meet these expectations, ANSES set up the SDHI Working Group (SDHI WG) following an open call for applications. Given the scope of the work covered by this expert appraisal, the WG reports to two expert committees: the one on "Plant protection substances and products, biocontrol" (CES Phyto BC) and the one on "Health reference values" (CES VSR).

The scale of the work, the time needed for the WG experts to familiarise themselves with the issue, and their desire to optimise their use of the content of both the regulatory dossiers and the scientific literature led the WG – which undertook a review of all the TRVs for 14 SDHI substances, i.e. a total of 39 TRVs – to request several extensions to the deadline that ANSES had set in its mandate. ANSES nevertheless set a final deadline of mid-2023 for the work of the various expert groups and committees to be concluded, i.e. two and a half years after the start of the WG's work.

Whether within the WG itself, or between the WG and the two CESs, the Agency notes that there was no systematic convergence on the scientific conclusions, even though a significant amount of time was devoted to debate. As stipulated in the fundamental principles of collective expert appraisal at ANSES, the Agency ensures transparency on points of non-convergence. Regarding the differences within the WG, this is done by including the dissenting positions in an annex to the report or opinion. The divergence between the WG and the two CESs is reflected in the wording of various parts of this opinion's Section 3, where the Agency notes that some parts of the report were not endorsed by one or other of the CESs (the WG's report having been examined by both ANSES expert committees (CESs) mentioned above).

The CES VSR validated all the TRVs proposed by the SDHI WG. However, it did not validate those parts of Chapter 6 relating to the points of concern raised by the WG concerning these substances. Nor did it validate Chapters 7 (SDH dysfunction, diseases and target organs) and 8 (Toxicity for each organ). Moreover, regarding the WG's recommendations, the CES VSR did not support a number of the research recommendations made.

The SDHI WG's report was validated by the CES on "Plant protection substances and products, biocontrol". However, regarding Chapter 7, a majority of experts abstained.

In addition, the WG's report included "personal contributions" containing further information relating to the questions in the request and which, for reasons of transparency, appear after the annexes to the report. They were made available to the CESs for information, although a lack of time prevented them from being validated by the entire WG, or by the CESs.

ANSES's position is therefore set out below.

ANSES's conclusions

The WG looked at 14 ASs from the SDHI class (13 fungicides and 1 acaricide). These are substances for which a European assessment was available at the time the WG conducted its work. The WG carried out a new analysis of the toxicity of these substances and produced recommendations for amending some of the TRVs used.

Regarding the TRVs, the Agency points out that for plant protection substances, three main TRVs are used, as defined in Section 3.1.1 of this opinion:

- the acceptable operator exposure level (AOEL);
- the acceptable daily intake (ADI);
- the acute reference dose (ARfD).

As part of its expert appraisal, the WG analysed the information that led to the establishment of the existing TRVs, focusing on:

- the quality of the key studies
- an analysis of the relevance of the selected critical effects
- the choice of the critical dose

It also assigned confidence levels to the confirmed TRVs or those subject to alternative proposals, applying the ANSES methodological guide (ANSES, 2017).

The WG considered that 11 of the 39 TRVs analysed needed to be revised. These proposals were based on a new analysis of the data available in the dossiers submitted for the approval of active substances under Regulation (EC) No 1107/2009, and data in the literature. The following reasons were given for adapting these values: a different choice of key study or critical dose (for example, a NOAEL[11] established in the dossier regarded as a LOAEL[12] by the WG), a different choice of critical effect, or uncertainties related to the quality of the key study.

[11] NOAEL – Highest dose at which no toxic or adverse effects is observed
[12] LOAEL – Lowest dose at which a toxic or adverse effect is observed

The WG's recommendations concerned the following TRVs and active substances:

- the AOELs for benzovindiflupyr, cyflumetofen and isofetamid

Substance	AOEL (mg/kg bw/d) harmonised at EU level	AOEL (mg/kg bw/d) WG's proposal	Rationale
Benzovindiflupyr	0.04	0.012	Decreased NOAEL
Cyflumetofen	0.11	0.07	Change in key study
Isofetamid	0.05	0.03	Change in key study

- the ADIs for carboxin, cyflumetofen, fluopyram, isopyrazam and penthiopyrad

Substance	ADI (mg/kg bw/d) harmonised at EU level	ADI (mg/kg bw/d) WG's proposal	Rationale
Carboxin	0.008	0.0027	The NOAEL was considered to be a LOAEL – addition of a safety factor of 3
Cyflumetofen	0.17	0.1	Change in key study
Fluopyram	0.012	0.004	Addition of a safety factor of 3 (uncertainty related to the data)
Isopyrazam	0.03	0.018	Safety factor of 3 instead of 2 (LOAEL – NOAEL)
Penthiopyrad	0.1	0.03	Change in key study Use of a LOAEL (addition of a safety factor of 3)

- the ARfDs for cyflumetofen, penflufen and pydiflumetofen

Substance	ARfD (mg/kg bw) harmonised at EU level	ARfD (mg/kg bw) WG's proposal	Rationale
Cyflumetofen	-	0.5	Change in key study
Penflufen	0.5	0.33	The NOAEL was considered to be a LOAEL – addition of a safety factor of 3
Pydiflumetofen	0.3	0.1	Change in key study

ANSES endorses these proposals by the WG. The Agency notes that these amendments lead to these TRVs being reduced by factors of between 1.5 and 3.3.

In light of these proposals, the Agency has adopted the following actions:

- **Benzovindiflupyr** (AOEL[13]) is currently being examined as part of the approval renewal procedure. France is the rapporteur Member State and Austria the co-rapporteur Member State. The proposal concerning the AOEL will be presented as part of the draft assessment report that will be sent to EFSA in 2024 and then submitted for public consultation prior to the peer review phase and publication of the assessment conclusions by EFSA.
- **Cyflumetofen** (AOEL, ADI, ARfD), **fluopyram** (ADI), **isofetamid** (AOEL) and **penthiopyrad** (ADI) are currently being examined as part of the approval renewal procedure. The draft assessment reports are expected to be sent to EFSA between 2023 and 2025. Proposals to amend the TRVs will be submitted as part of the public consultation on the draft assessment reports.
- **Pydiflumetofen** (ARfD) is currently being examined as part of the approval procedure. France is the rapporteur Member State and Austria the co-rapporteur Member State. In the initial draft report submitted for public consultation, the proposed ARfD was set at 0.1 mg/kg bw. Following the public consultation and peer review phase, this value was changed to 0.3 mg/kg bw. This value was adopted in EFSA's conclusions[14]. It is proposed to maintain the value of 0.3 mg/kg bw set in a recent European assessment.
- For carboxin (ADI) and isopyrazam (ADI), no action is deemed necessary as the substances are no longer approved under Regulation (EC) No 1107/2009.
- For penflufen (ARfD), no action is seen as a priority since expiry of the substance's approval under Regulation (EC) No 1107/2009 has already been set for 31/05/2025.

Regarding the epidemiological data, Inserm's expert appraisal (2021) found that there were still virtually no epidemiological data on the effects of SDHI active substances on the health of the occupationally-exposed or the general population. The literature search conducted by the experts did not identify any additional data.

As well as the above-mentioned conclusions and actions relating to TRVs, ANSES noted the following from the experts' analysis of the toxicological and mechanistic data.

With regard to the "points of concern" highlighted by the WG in its conclusions and recommendations concerning the TRVs, the Agency considers – like the CES VSR – that while they may be useful in guiding methodological deliberations or future investigations into the mode of action of SDHI substances in general, they do not constitute challenges to the TRVs.

Moreover, ANSES stresses that this analysis was unable to distinguish between the health consequences related to permanent inactivation (such as may be caused by genetic deficiencies) and those of SDH inhibition by xenobiotics such as SDHIs used as plant protection products (which may vary in extent and be temporary).

[13] The brackets are used to indicate the type of revised TRV, which will be the focus of the information measures by European stakeholders.
[14] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2019.5821

ANSES's methodological and research recommendations

ANSES endorses the following methodological and research recommendations:

- **Continue improving knowledge of the mechanism of action of SDHIs and its health consequences**:
    - **by developing a sequential testing strategy to assess mitotoxic potential and its functional consequences;**
    - **by improving knowledge of pharmacokinetics in order to facilitate the use of *in vitro* toxicological data;**
    - **by encouraging the development of adverse outcome pathways (AOPs)**. This is because AOPs can be used to identify a sequential chain of events connected by a causal link at different levels of biological organisation, leading to an adverse health effect or an ecotoxicological effect.

These issues could be raised with the OECD and EFSA in order to define test strategies and study protocols, including criteria for interpreting the results, which could be used in the context of the assessments.

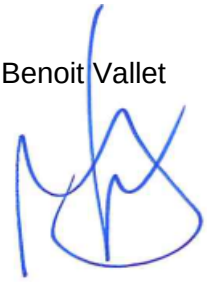
- **Improve knowledge of population exposure levels to SDHIs.** ANSES has already included the identification of four SDHI ASs in its third total diet study (TDS) currently being deployed. With regard to future monitoring studies, it will explore the possibility of including SDHI ASs in the studies it leads, and will approach partners supporting this type of study.

The Agency also refers to its other opinion on the cumulative exposure of French consumers to SDHI substances (internal request 2019-SA-0135). This retrospective assessment of cumulative risks was carried out using two different cumulative risk assessment methods, one deterministic and the other probabilistic. **It concluded that no unacceptable risk is expected for French consumers, within the meaning of Regulation (EC) No 546/2011, associated with chronic exposure to active substances in the SDHI class, even using the TRVs proposed by the WG.**

In addition, with regard to sub-populations at risk, after having financed the feasibility study, ANSES is continuing deployment of a study on the impact of environmental exposure on tumour risk in subjects at risk of hereditary SDH-related paraganglioma (the PGL Expo study) using epidemiological data.

- **Improve knowledge of the potential effects of SDHIs on ecosystems and their impact on biodiversity**. In this respect, it should be noted that substances in the SDHI class could be addressed in the future European project on environmental risk assessment led by EFSA: PERA – Advancing the Environmental Risk Assessment of Plant Protection Products towards a system-based approach.

Pr Benoit Vallet



KEY WORDS

Inhibiteurs de la succinate deshydrogénase (SDHI), substances phytopharmaceutiques, mitochondrie, santé humaine, valeurs toxicologiques de référence

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SUGGESTED CITATION

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ANNEX 1

Presentation of the participants

PREAMBLE: The expert members of the Expert Committees and Working Groups or designated rapporteurs are all appointed in a personal capacity, *intuitu personae*, and do not represent their parent organisation.

WORKING GROUP

Chair

Mr Claude EMOND – Associate Professor at the University of Montreal – Environmental and occupational risk assessment, nanoparticles, mixture interaction, PBPK, pharmacokinetics

Members

Mr Thierry BARON – Head of the Neurodegenerative Diseases Unit at ANSES – Neurotoxicity, neurodegenerative diseases, prions, experimental animal models

Ms Sylvie BORTOLI – Research Engineer at Paris Cité University – Mechanistic toxicology, metabolic reprogramming, cancer, mitochondrial dysfunction, energy metabolism and diseases

Mr Frédéric BOUILLAUD – Research Director at the National Institute of Health and Medical Research (Inserm) – Mitochondria, bioenergetics (until 01/11/2022)

Mr Thomas CLAUDEPIERRE – University Professor – Neuroscience, neurodegenerative diseases, primary neuronal culture, behavioural phenotyping, retina, neuroprotection

Ms Fatima DJOUADI – Research Director at Inserm – Mitochondrial oxidative metabolism, fatty acid oxidation, respiratory chain, mitochondrial regulation (until 31/12/2022)

Mr Jérôme HENRI – Research Project Leader at ANSES – ADME, *in vitro* toxicology, PBPK, animal experimentation

Ms Laurence HUC – Research Director at the National Research Institute for Agriculture, Food and the Environment (INRAE) – Environmental carcinogenesis, food toxicology, mitotoxicity, oxidative stress, energy metabolism, cellular mechanisms of toxicity

Mr Anthony LEMARIE – Lecturer, Clinical and Metabolic Biochemistry at the University of Toulouse – Mitochondrial metabolism, brain tumours, cancer stem cells, radiobiology, resistance mechanisms, carcinogenesis, succinate dehydrogenase

Ms Béatrice MORIO-LIONDORE – Research Director at INRAE – Mitochondria, mitochondria-associated ER membranes (MAMs), chronic non-transmissible metabolic diseases, physiology, ageing, translational research (until 20/12/2022)

Mr Jean-Ulrich MULLOT – Chief Pharmacist, Head of the Navy Surveillance Analysis and Expertise Laboratory (LASEM) – Regulatory toxicology, chemical product regulation, quantitative health risk assessment

Mr Luc MULTIGNER – Research Director at Inserm – Epidemiology, pesticides, endocrine disruptors, reproduction, fertility, hormone-dependent cancers

Mr Rodrigue ROSSIGNOL – Research Director at Inserm – Mitochondria, bioenergetics, rare diseases, cancer, mitochondrial therapy, mitochondrial toxicity

Mr Bernard SALLES – Professor Emeritus at the University of Toulouse – Toxicology, carcinogenesis, nanotoxicology, *in vitro/vivo* models

Mr Ludovic WROBEL – Research Biologist – Oncology, neurobiology, neurotoxicity, immunotoxicity, cellular respiration

EXPERT COMMITTEE

- CES on "Plant protection substances and products, biocontrol"

Chair

Mr Jean-Ulrich MULLOT – Military Pharmacist (Military Health Service). Speciality: Toxicology, risk assessment, regulations, radionuclides, analytical chemistry

Vice-Chair

Mr Christian GAUVRIT – Retired from the French National Institute for Agronomic Research (INRA). Speciality: Efficacy, herbicides, plant physiology, adjuvants, formulants

Members

Mr Marc BARDIN – Research Director at INRAE. Speciality: Efficacy, biocontrol, phytopathology, microbiology

Mr Enrique BARRIUSO – Research Director at INRAE. Speciality: Environment, fate, transfers, soil, chemistry

Mr Philippe BERNY – Teacher – Researcher (VetAgro Sup). Speciality: Ecotoxicology, birds and mammals

Ms Marie-France CORIO-COSTET – Research Director at INRAE. Speciality: Efficacy, fungicides, herbicides, vines, resistance, plant defence stimulators, biocontrol

Mr Jean-Pierre CUGIER – Retired from the Ministry of Agriculture, Senior Scientific Officer (European Food Safety Authority) until 30/09/2016. Speciality: Residues and consumer safety

Mr Marc GALLIEN – Project Officer, Agricultural Mutual Insurance Scheme (MSA). Speciality: Application of plant protection products, exposure of operators and workers, analysis of the consequences on human health of exposure to plant protection products

Ms Sonia GRIMBUHLER – Researcher at INRAE. Speciality: Assessment of farm worker exposure, agricultural machinery, field measurement

Ms Guillermina HERNANDEZ RAQUET – Research Director at INRAE. Speciality: Microbiology, microbial ecology, biodegradation, analytical chemistry, persistent pollutants, ecotoxicology, biotechnology

Mr François LAURENT – Research Officer at INRAE. Speciality: Metabolism, organic compound residues, environmental contamination, plant physiology

Ms Laure MAMY – Research Director at INRAE. Speciality: Environmental fate of pesticides, modelling

Mr Patrick SAINDRENAN – Retired from the National Centre for Scientific Research (CNRS). Speciality: Phytopathology, fungicides, plant defence stimulators, modes of action, biocontrol, metabolism of pesticide residues in plants

Ms Jeanne STADLER – Toxicology Consultant, Retired from the Pfizer Research Centre. Speciality: Reproductive toxicology

- CES on "Health reference values" (CES VSR)

Chair

Mr Fabrice MICHIELS – Occupational Physician/Toxicologist – Corrèze and Dordogne occupational health & prevention service (SPST 19-24) – Expertise: occupational medicine, toxicology

Vice-Chair

Ms Anne MAITRE – University Professor-Hospital Practitioner at the Laboratory of Occupational and Environmental Toxicology, Grenoble University Hospital; Manager of the "Environment and population health forecasting" team, TIMC Laboratory, Grenoble-Alpes University – Expertise: medicine, toxicology, biomarkers of exposure, pollutant metrology, industrial hygiene – Resigned in March 2023

Mr Jérôme THIREAU – PhD, Research Officer at CNRS – Expertise: Animal physiology, electrophysiology, cell biology, cardiotoxicity – From May 2023

Members

Mr Luc BELZUNCES – Research Director and Director of the Laboratory of Environmental Toxicology at INRAE – Expertise: general toxicology, neurotoxicology, ecotoxicology, analytical chemistry, risk assessment

Ms Michèle BISSON – Toxicologist and Research Manager at the National Institute for Industrial Environment and Risks (Ineris) – Expertise: Pharmacist-Toxicologist, toxicity reference values, health risk assessment

Ms Céline BOTINEAU – Engineer in Chemical Risk Prevention at the French Alternative Energies and Atomic Energy Commission (CEA) – Expertise: industrial hygiene, chemistry, risk assessment – Resigned in November 2022

Ms Anne CHEVALIER – Retired from the French Institute for Public Health Surveillance – Expertise: epidemiology

Mr François CLINARD – Epidemiologist at *Santé Publique France* – Expertise: pharmacy-toxicology, epidemiology, health risk assessment – Resigned in May 2023

Ms Fatiha EL-GHISSASSI – Scientist, Monographs Programme. Evidence Synthesis and Classification Branch. International Agency for Research on Cancer (IARC) – Expertise: biochemistry specialising in carcinogenesis and genotoxicity

Mr Claude EMOND – Associate Professor – School of Public Health, University of Montreal – Department of Environmental and Occupational Health – Expertise: toxicology, PBPK modelling, toxicokinetics, nanotoxicology, endocrine disruptors

Mr Robert GARNIER – Medical Toxicologist, Paris – Expertise: medical toxicology, occupational health, environmental health

Ms Perrine HOET – Professor at the Catholic University of Louvain, IREC – Expertise: occupational medicine, occupational and environmental toxicology – Resigned in February 2023

Mr Kevin HOGEVEEN – Toxicologist, ANSES Fougères, Toxicology of Contaminants Unit – Expertise: toxicology, genotoxicity, hepatotoxicity, *in vitro* toxicology

Ms Yuriko IWATSUBO – Doctor-Epidemiologist at *Santé Publique France* – Expertise: epidemiology of occupational risks

Mr Frédéric LIRUSSI – University Professor-Hospital Practitioner at the Health Sciences Training & Research Unit and Besançon University Hospital – Expertise: clinical toxicology, analytical toxicology, innate immunity, reprotoxicity – Resigned in March 2023

Mr Luc MULTIGNER – Research Director, Inserm U1085 IRSET – Expertise: epidemiology, endocrine disruptors, diseases of reproductive functions and organs

Ms Nadia NIKOLOVA-PAVAGEAU – Medical Advisor at the National Research and Safety Institute (INRS) – Expertise: occupational medicine, medical toxicology, biomarkers of exposure

Mr Benoît OURY – Research Manager at INRS – Expertise: atmospheric metrology, workplace air, occupational exposure assessment

Mr Henri SCHROEDER – Lecturer at the Faculty of Science and Technologies of the University of Lorraine, Neurosciences & Animal Biology Department and Inserm unit U1256 Nutrition, Genetics and Exposure to Environmental Risks; Pharmacist-Neurobiologist – Expertise: neurotoxicity, environmental pollutants, animal behaviour, brain development, perinatal exposure

Mr Olivier SORG – Research Group Head at the University of Geneva – Expertise: doctor of science in biochemistry, experimental toxicology, dermatotoxicology

Mr Jérôme THIREAU – PhD, CNRS Research Manager – Expertise: animal physiology, electrophysiology, cell biology, cardiotoxicity – Member of the CES until April 2023 then Vice-Chair

Ms Maeva WENDREMAIRE – Lecturer at the University of Burgundy – Expertise: toxicology, reprotoxicity, pharmacology, analytical toxicology

HEARINGS WITH EXTERNAL PERSONS

Department of Nephrology and Organ Transplant; Reference Centre for Rare Kidney Diseases; Toulouse University Hospital – Inserm U1297 (Institute of Metabolic and Cardiovascular Diseases) Toulouse III University

Mr Stanislas FAGUER – MD, PhD, University Professor – Hospital Practitioner

ANNEX 2

Formal request letter

anses
agence nationale de sécurité sanitaire alimentation, environnement, travail
Connaître. évaluer. protéger

2019-SA-0202

Decision no. 2019-12-333

INTERNAL REQUEST

The Director General of the French Agency for Food, Environmental and Occupational Health & Safety (ANSES),

Having regard to the Public Health Code, and in particular its Article L.1313-3 giving ANSES the prerogative to issue an internal request on any question with a view to accomplishing its missions,

Has decided:

Article 1 – The French Agency for Food, Environmental and Occupational Health & Safety is issuing an internal request to conduct an expert appraisal whose characteristics are listed below.

1.1 Themes and objectives of the expert appraisal

ANSES is issuing a new internal request to update the data from the scientific literature published since the succinate dehydrogenase inhibitor (SDHI) fungicides were approved, in order to determine whether there is any new evidence that might call for an update of the opinion and report of the collective expert appraisal group[15], and justify a change in the assessments conducted on the SDHI class of substances at European level.

1.2 Background of the internal request

Following the alert issued by a group of scientists, in May 2018 ANSES commissioned an emergency collective expert appraisal group (GECU) to determine whether "*the scientific information and hypotheses provided by the authors [of the] article... provided... evidence demonstrating exposure and risks that had not been taken into account in the assessments of the active substances concerned*". The Agency's opinion based on this expert appraisal was published in January 2019[16].

[15] OPINION of the French Agency for Food, Environmental and Occupational Health & Safety on the "assessment of a warning signal regarding the toxicity of succinate dehydrogenase inhibitor (SDHI) fungicides".
[16] 5 January 2019

Moreover, ANSES informed the European and North American authorities and other Member States, calling for vigilance, and asked Inserm to take account of the SDHI issue in its ongoing collective expert appraisal on the impact of pesticides.

In addition, ANSES issued an internal request on the cumulative risks to consumers associated with exposure to SDHIs. The results are expected in March 2020.

ANSES has also facilitated and funded new research projects. And through the monitoring schemes coordinated by phytopharmacovigilance, it seeks to detect any health effects of SDHIs that may be observed in the field.

Following this, ANSES identified various recently published data or studies, including the publication by Benit *et al.* in PLOS One, which will need to be analysed. The above-mentioned collective expert appraisal report by Inserm should also be taken into account.

To respond to the internal request, an ad hoc working group (WG) will be set up from the Agency's pool of experts (existing groups and other sources of competent individuals). This group's conclusions will be validated by the lead CESs.

1.3 Questions on which the expert appraisal work will focus

The following questions will be examined:

- Should the analysis of available or future information, mainly concerning critical effects, lead to the toxicity reference values for substances being adapted? In this respect, particular attention should be paid to the mitochondrial toxicity of active substances in the SDHI class;

  Do the results of vigilance, monitoring or epidemiological studies provide information suggesting a health impact that has not been taken into account in the risk assessment for these substances?
- In light of this information, are amendments to the toxicity reference values for SDHI active substances necessary? If so, proposals should be made so that they can be presented at European level.

1.4 Estimated duration of the expert appraisal

The final conclusions will have to be delivered within 12 months, and an interim opinion on the need to update the GECU's opinion of January 2019 is expected within six months.

Article 2 – An opinion will be issued and published by the Agency following completion of the work.

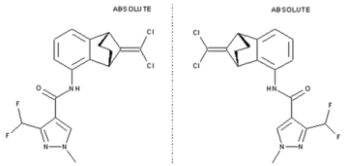
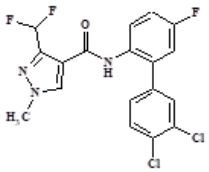
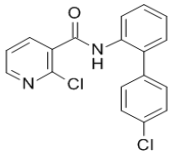
Signed in Maisons-Alfort on 06 DEC. 2019

Dr Roger Genet

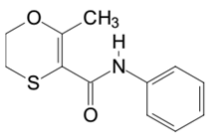
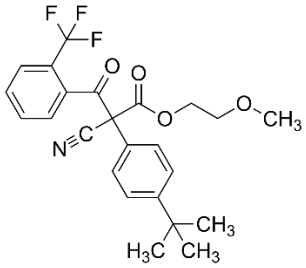
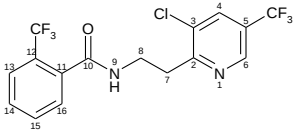
Director General

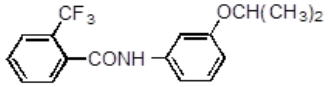
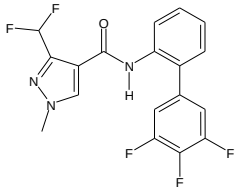
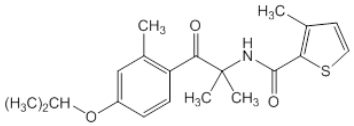
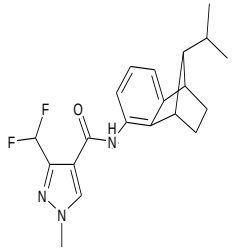
ANNEX 3

Table 1: Identity and EU regulatory status of the SDHIs considered in the expert appraisal

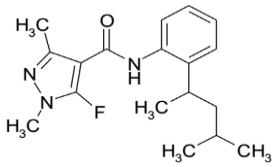
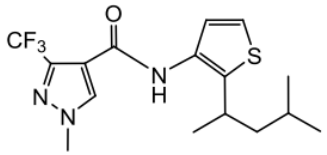
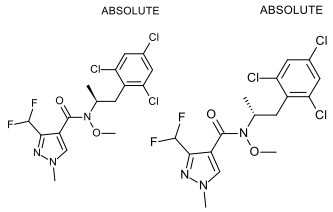
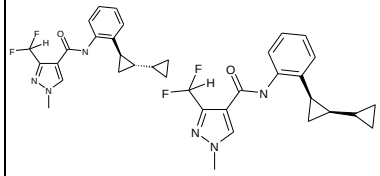
SDHI list (source: FRAC and IRAC)	CAS number	Chemical class	Chemical structure	Main types of use in France (E-Phy, 24/04/2023)	End date of AS approval[17]	Harmonised classification and RAC opinions[18]
Benzovindiflupyr	1072957-71-1	Pyrazole-4-carboxamide		Treatment of aerial parts: cereals, turf (greens and tees on golf courses)	Approved 02/03/2024	Acute Tox 3 – H301 / H331 Aquatic Acute 1 – H400 Aquatic Chronic 1 – H410 (ATP9; 2016)
Bixafen	581809-46-3	Pyrazole-4-carboxamide		Treatment of aerial parts: cereals, cruciferous oilseed crops	Approved 31/05/2025	No classification
Boscalid **(former name: nicobifen)**	188425-85-6	Pyridine-carboxamide		Treatment of aerial parts: cereals, vines, orchards, cruciferous oilseed crops, protein crops, pulses, soy, sunflower, flax, vegetables, seed-bearing crops	Approved 15/04/2026	No classification

[17] AS: active substance
[18] the RAC opinions have been provided where these have not yet been implemented in the CLP Regulation.

Carboxin	5234-68-4	Oxathiin carboxamide		Seed treatment: cereals	Not approved 31/05/2021	Skin Sens. 1 – H317 STOT RE 2 – H373 (kidneys) Aquatic Acute 1 – H400 Aquatic Chronic 1 – H410 (ATP14; 2019)
Cyflumetofen	400882-07-7	Benzoylacetonitrile		Acaricide Treatment of aerial parts: flower crops, green plants and strawberry plants (only authorised in soil-less production under shelter)	Approved 31/10/2025	Carc. 2 – H351 Skin Sens. 1A – H317 (ATP14; 2019)
Fluopyram	658066-35-4	Pyridinyl-ethyl-benzamide		Treatment of aerial parts: cereals, arboriculture, vegetable crops, oilseed crops, bananas, turf (golf courses and sports fields) Soil treatment: vegetable and ornamental crops (fungicide and nematicide use)	Approved 31/01/2024	Aquatic Chronic 2 – H411 (ATP9; 2016)

Flutolanil	66332-96-5	Phenyl-benzamide		Treatment of tubers/seeds: potatoes	Approved 29/02/2024	No classification
Fluxapyroxad	907204-31-3	Pyrazole-4-carboxamide		Treatment of seeds and aerial parts: cereals, orchards, vegetable crops, seed-bearing crops Soil treatment: potatoes	Approved 31/05/2025	Lact. – H362 Aquatic Acute 1 – H400 Aquatic Chronic 1 – H410 (ATP15; 2020)
Isofetamid	875915-78-9	Phenyl-oxo-ethyl thiophene amide		Treatment of aerial parts: vines, orchards, strawberry plants, herbs, lettuce, cruciferous oilseed crops	Approved 15/09/2026	No classification
Isopyrazam	881685-58-1	Pyrazole-4-carboxamide		Treatment of aerial parts: ornamental plants (deadline for withdrawal of product MAs[19] by Member States: 08/09/2022)	Not approved 08/06/2022	Carc. 2 – H351 Repr. 1B – H360D Skin Sens. 1B – H317 Aquatic Acute 1 – H400 Aquatic Chronic 1 – H410 (ATP18, 2022)

[19] MA: Marketing authorisation

Penflufen	494793-67-8	Pyrazole-4-carboxamide		Treatment of tubers/seeds: potatoes No product authorised in France	Approved 31/05/2025	Carc. 2 – H351 Aquatic Acute 1 – H400 Aquatic Chronic 1 – H410 (ATP15; 2020)
Penthiopyrad	183675-82-3	Pyrazole-4-carboxamide		Treatment of aerial parts: cereals, vegetable crops, strawberries, fruit trees Seed treatment: beets	Approved 31/05/2025	Aquatic Acute 1 – H400 Aquatic Chronic 1 – H410 (ATP10; 2017)
Pydiflumetofen	1228284-64-7	N-methoxy-(phenylethyl)-pyrazole-carboxamide			Approval application in progress	Carc. 2 – H351 Repr. 2 – H361f Aquatic Acute 1 – H400 Aquatic Chronic 1 – H410 (ATP17; 2021)
Sedaxane	874967-67-6	Pyrazole-4-carboxamide		Seed treatment: cereals, beets and maize	Approved 31/05/2025	Carc. 2 – H351 Aquatic Acute 1 – H400 Aquatic Chronic 2 – H411 (ATP17; 2021)

ANNEX 4

Table 2: Establishment of current AOELs and those selected by the WG

Substance	Regulatory dossier				WG conclusion based on current data			
	Critical effect (key study)	**Critical dose (mg/kg bw/d)**	**Uncertainty factor (oral absorption)**	**Current AOEL (mg/kg bw/d)**	**Critical effect (key study)**	**Critical dose (mg/kg bw/d)**	**Uncertainty factor (oral absorption)**	**AOEL (mg/kg bw/d) Confidence level**
Benzovindiflupyr	↓ in body weight, hypertrophy of the liver, pituitary gland and zona glomerulosa of the adrenal glands in the parents Abnormal sperm, ↓ in growing ovarian follicles and corpora lutea and ↑ in incidence of lactational dioestrus In young: ↓ in body weight, ↑ in liver weight and delayed sexual maturation in males (2-generation study in rats)	6.8	100 (60%)	0.04	↓ in sperm motility, ↑ in incidence of lactational dioestrus, ↓ in liver glycogen deposition (2-generation study in rats)	1.2	100 (no correction for oral absorption)	**0.012** Moderate-low
Bixafen	Hypertrophy of the liver and thyroid follicular cells (90-day study in rats)	12.9	100 (no correction for oral absorption)	**0.13**	Maintain current TRV Confidence level: moderate-high			
Boscalid	Weight loss, liver effects (increased weight and altered clinical chemistry), increased thyroid weight (1-year study in dogs)	22	100 (44%)	**0.1**	Maintain current TRV Confidence level: moderate-high			
Carboxin	Kidney damage (chronic nephropathy) (90-day study in rats)	5.5	100 (no correction for oral absorption)	**0.055**	Maintain current TRV Confidence level: moderate-high			
Cyflumetofen	Effects on the adrenal cortex and ovaries (90-day and 2-year studies in rats)	17	100 (68%)	0.11	Effects on the adrenal cortex (2-generation study in rats)	10	100 (68%)	**0.07** Moderate

Fluopyram	Liver effects (including effects on weight, clinical chemistry and histology) (90-day study in mice)	5.4	100 (no correction for oral absorption)	**0.05**	Maintain current TRV Confidence level: low			
Flutolanil	Increased relative weight of the thyroid and parathyroid glands (males) (90-day study in rats)	37	100 (70%)	**0.26**	Maintain current TRV Confidence level: moderate-high			
Fluxapyroxad	Liver effects (increased weight, hypertrophy) (90-day study in rats)	6	100 (68%)	**0.04**	Maintain current TRV Confidence level: moderate			
Isofetamid	Decreased body weight. Liver effects (including increased liver weight, increased alkaline phosphatases and hypertrophy) (1-year study in dogs)	5.34	100 (no correction for oral absorption)	0.05	Same liver effects selected (90-day study in dogs)	2.95	Same as regulatory dossier	**0.03** Moderate
Isopyrazam	Effects on body weight and liver (increased weight and hypertrophy) (multi-generational study in rats)	8	100 (64%)	**0.05**	Maintain current TRV Confidence level: moderate			
Penflufen	Liver hypertrophy (1-year study in dogs)	7.7	100 (no correction for oral absorption)	**0.077**	Maintain current TRV Confidence level: moderate			
Penthiopyrad	Effects on weight, liver and adrenal glands in the P and F1 generations. (multi-generational study in rats)	11	100 (no correction for oral absorption)	**0.1**	Maintain current TRV Confidence level: Moderate			
Pydiflumetofen	Increased skeletal variations in the foetus (prenatal developmental toxicity study in rabbits)	10	100 (no correction for oral absorption)	**0.1**	Maintain current TRV Confidence level: moderate			
Sedaxane	Reduced body weight, reduced grip strength (90-day study in rats)	28	100 (no correction for oral absorption)	**0.28**	Maintain current TRV Confidence level: moderate			

Table 3: Establishment of current ADIs and those selected by the WG

Substance	Regulatory dossier				WG conclusion based on current data			
	Critical effect (key study)	**Critical dose (mg/kg bw/d)**	**Uncertainty factor**	**Current ADI (mg/kg bw/d)**	**Critical effect (key study)**	**Critical dose (mg/kg bw/d)**	**Uncertainty factor**	**ADI (mg/kg bw/d) Confidence level**
Benzovindiflupyr	↓ in body weight gain, liver effects (including hypertrophy and vacuolisation) and thyroid effects (adenoma) (2-year study in rats)	4.9	100	**0.05**	Maintain current TRV Confidence level: moderate			
Bixafen	Effects on the liver (including hypertrophy and increased cholesterol) and thyroid (altered colloid) (2-year study in rats)	2	100	**0.02**	Maintain current TRV Confidence level: moderate			
Boscalid	Effects on the liver, changes in haematology and clinical chemistry parameters (2-year study in rats)	4.4	100	**0.04**	Maintain current TRV Confidence level: moderate-high			
Carboxin	Fibrous osteodystrophy of the femur and parathyroid hyperplasia (2-year study in rats)	0.82	100	0.008	Same as regulatory dossier	Challenged the NOAEL of 0.82 mg/kg bw/d as a LOAEL	300	**0.0027** Moderate
Cyflumetofen	Effects on the adrenal cortex and ovaries (90-day and 2-year study in rats)	17	100	0.17	Effects on the adrenal cortex (2-generation study in rats)	10	100	**0.1** Moderate
Fluopyram	Effect on the liver and thyroid (including hypertrophy) and on the kidneys (degenerative effects) (2-year study in rats)	1.2	100	0.012	Same as regulatory dossier	1.2	300	**0.004** Low
Flutolanil	Histological changes in the spleen, with a decreased number of splenocytes (males) and decreased haemoglobin levels (females) (2-year study in rats)	8.7	100	**0.09**	Maintain current TRV Confidence level: Moderate-high			

Fluxapyroxad	Effects on the liver (including hepatocellular hypertrophy and adenomas) (2-year study in rats)	2.1	100	**0.02**	Maintain current TRV Confidence level: Moderate-high			
Isofetamid	Reduction in weight and in body weight gain (1-year study in dogs)	1.57	100	**0.02**	Maintain current TRV Confidence level: Moderate			
Isopyrazam	Effect on the liver (including hypertrophy) (2-year study in rats)	No NOAEL LOAEL = 5.5	200	0.03	Same as regulatory dossier	Same as regulatory dossier	300 (LOAEL-NOAEL)	**0.018** Moderate-low
Penflufen	Effects on the liver (including hypertrophy) and thyroid (including altered colloid) (2-year study in rats)	4	100	**0.04**	Maintain current TRV Confidence level: Moderate-high			
Penthiopyrad	Effect on body weight, adrenal glands and liver in the parental generations (multi-generational study in rats)	11	100	0.1	Effects on kidneys (2-year study in rats)	No NOAEL LOAEL = 9	300 (LOAEL-NOAEL)	**0.03** Moderate
Pydiflumetofen	Reduction in body weight and effects on the liver (histological lesions) (18-month study in mice)	9.2	100	**0.09**	Maintain current TRV Confidence level: Moderate			
Sedaxane	Reduced body weight, effects on the liver and thyroid (2-year study in rats)	11	100	**0.11**	Maintain current TRV Confidence level: Moderate-low			

Table 4: Establishment of current ARfDs and those selected by the WG

Substance	**Regulatory dossier**				**WG conclusion based on current data**			
	Critical effect (key study)	**Critical dose (mg/kg bw)**	**Uncertainty factor**	**Current ARfD (mg/kg bw)**	**Critical effect (key study)**	**Critical dose (mg/kg bw)**	**Uncertainty factor**	**ARfD (mg/kg bw) Confidence level**
Benzovindiflupyr	Clinical observations of neurotoxicity (↓ in grip strength, motor activity, temperature), ↓ in body weight gain (acute neurotoxicity study in rats)	10	100	**0.1**	Maintain current TRV Confidence level: moderate			
Bixafen	Reduced maternal and foetal weight (prenatal developmental toxicity study in rats)	20	100	**0.2**	Maintain current TRV Confidence level: Moderate			
Boscalid	The toxicological profile does not justify determining an ARfD				The WG agreed with this conclusion.			
Carboxin	The toxicological profile does not justify determining an ARfD				The WG agreed with this conclusion.			
Cyflumetofen	The toxicological profile does not justify determining an ARfD				Delayed ossification (prenatal developmental toxicity study in rats)	50	100	**0.5** Moderate
Fluopyram	Decreased locomotor and motor activity (acute neurotoxicity study in rats)	5	100	**0.5**	Maintain current TRV Confidence level: Moderate			
Flutolanil	Resorption and foetal mortality (prenatal toxicity study in rabbits)	40	100	**0.4**	Maintain current TRV Confidence level: Moderate			

Fluxapyroxad	Developmental effects in rabbits (post-implantation losses), reduced maternal weight and reduced maternal weight gain in rats (prenatal toxicity study in rats and rabbits)	25	100	**0.25**	Maintain current TRV Confidence level: moderate			
Isofetamid	Reduced maternal food consumption. Increased skeletal variations in foetuses. (prenatal toxicity study in rabbits)	100	100	**1**	Maintain current TRV Confidence level: moderate-high			
Isopyrazam	Reduced maternal weight gain (prenatal toxicity study in rats)	20	100	**0.2**	Maintain current TRV Confidence level: moderate			
Penflufen	Decreased locomotor activity (in the initial acute neurotoxicity study in rats) (acute neurotoxicity study in rats – follow-up study)	50	100	0.5	Decreased locomotor activity (acute neurotoxicity study in rats – initial study)	No NOAEL LOAEL = 100	300 (LOAEL-NOAEL)	**0.33** Low-moderate
Penthiopyrad	Decreased foetal weight. (prenatal developmental toxicity study in rabbits)	75	100	0.75	Maintain current TRV Confidence level: moderate-high			
Pydiflumetofen	Reduced maternal weight gain and food consumption. (prenatal developmental toxicity study in rats)	30	100	0.3	Skeletal variations in the foetus (prenatal toxicity study in rabbits)	10	100	**0.1** Moderate
Sedaxane	Clinical signs, reduced locomotor activity and grip strength (acute neurotoxicity study in rats)	30	100	**0.3**	Maintain current TRV Confidence level: moderate			

ANNEX 5

Dissenting opinion on the conduct of the SDHI WG's expert appraisal

Laurence Huc, Anthony Lemarié

Improper evaluation of SDHI organ toxicity at the end of the expert appraisal

Objective: On 14 January 2022, after examining all the dossiers, the WG members agreed to conduct a cross-sectional analysis of the toxic effects of SDHIs. This analysis, which was innovative compared with the regulatory substance-by-substance assessment, sought to explain the organ toxicities that were common to or different for all the SDHIs assessed. This is essential for identifying the adverse effects common to substances with the same pharmacological target: SDH.

Method: In order to deal with these aspects consistently, a collective approach was followed for the analysis work. Each pair or trio of experts that examined an AS reported the toxic effects observed in the regulatory dossier (liver, kidneys, endocrine disruption, reprotoxicity, neurotoxicity, development, eye diseases, adrenal damage, thyroid damage, other) in a table with multiple rows and columns. Volunteer members then took all the table information for a given type of toxicity and summarised it by toxic effect for all the SDHIs. For example, in the case of renal toxicity, thyroid toxicity, ophthalmic effects, adrenal effects and endocrine disruption, the information in the table was taken and then checked again in the dossiers themselves, at source, to ensure that all the information had indeed been reported. To explain why the experts had focused on these toxic effects, several members provided a literature update on the state of the art on SDH and the organ/function in question.

Result: This cross-sectional analysis, which consisted in identifying a toxic effect that was more or less common to all SDHIs, revealed numerous examples of damage shared by the SDHIs involving the kidneys, endocrine disruption, neurotoxicity, eye diseases, adrenal, cardiac, liver and thyroid damage.

Use of results: Once completed, this collective work was not placed on the agenda early enough to be discussed, even though the duration of the expert appraisal would have enabled this to be done. Moreover, the resignation of three experts, who were closely involved in developing these cross-cutting sections, led some WG members to attribute less value to them. In the end, some of these sections, including the important part on endocrine disruption, were relegated to annexes presented as "personal contributions". Others, having benefited from neither a pluralistic and adversarial debate nor sufficient time, restated the regulatory literature in an unbalanced way compared with the academic literature. The analysis that had initially been worked on collectively was therefore clearly undervalued, if not invisible, and was not informed by all the scientific knowledge on mitotoxicity.

The cross-cutting section on the liver was not discussed at a meeting until February 2023, even though a bibliographic imbalance in this section had been reported when the full report was reviewed in September 2022. This section did not include any academic literature on SDH. On the other hand, it included literature in which the authors or funders had conflicts of interest related to the subject (agrochemical firms marketing the products, think-tanks funded by manufacturers) and which put forward arguments considering liver damage to be irrelevant for humans. This methodological bias was not really discussed in the meetings.

The sections on endocrine disruption, renal toxicity, neurotoxicity, adrenal glands and ocular toxicity were reviewed collectively by the WG (September and November 2022). Some of these contributions were then placed in annexes and presented as personal contributions, which had the effect of destructuring the report, making it lose its scientific consistency and minimising the contribution of the skills expressly mobilised for the expert appraisal.

Discussion: In a multi-disciplinary collective expert appraisal, it is unusual for each expert to sign their own part and for these parts to be placed end to end, as it should rather be the product of joint intelligence and work. The cross-sectional collective analysis was therefore an integral part of the WG's intentions, and then of the preliminary report reviewed and agreed by the WG in September 2022. Not being able to collectively discuss the summary of these parts and/or relegating them to annexes presented as personal contributions was contrary to the WG's initial intentions and above all underrated the results obtained.

Consequences: Understating this cross-sectional analysis reduced the scope of the collective expert appraisal and focused the results on the purely regulatory issue of analysing TRVs. However, the WG's scientific ambition was not to limit itself to these regulatory aspects but to take a broader view of the SDHI issue. In particular, there is a need for an integrated study of the way in which taking account of mitoxicity calls into question the framework for analysing TRVs.

A request reduced to almost exclusively regulatory aspects

Hearings refused: Discussions at the meetings mainly focused on the TRVs and very little on the cross-cutting sections. Proposals for hearings with experts from outside the WG who might have provided insights on missing skills (in hepatology, rare mitochondrial diseases, SDH-related cancers, thyroid damage) were all rejected by the coordination team according to rules that were difficult to understand – with the exception of one expert specialising in kidney diseases. A request to interview a member of ANSES's Scientific Board on the subject of its report on the credibility of scientific expert appraisals was rejected, despite the fact that difficulties encountered in the WG echoed points that had been addressed by the recommendations in the Scientific Board's report, particularly concerning the integration of scientific knowledge outside the regulatory framework.

Epistemic block: The CES VSR followed usual practice in its recommendation: "*The methodology usually adopted in the CES's work involves only taking account of effects that are relevant to health and present a statistically significant variation, and for which the dose-response relationship is not inconsistent*". This triple condition effectively excluded the diseases associated with SDH described in the literature: microphthalmia, pheochromocytomas, adrenal cortical damage and sometimes renal toxicity. It excluded rare diseases, whose incidence may increase. This epistemic block therefore prevented the full body of scientific knowledge from being taken into account.

Scientific supervision of the CES VSR and CES Phyto BC

The experts of the CES VSR and CES Phyto BC to which the WG reports have no particular expertise in SDHIs and did not examine all the regulatory dossiers in detail. This is why a specific WG was set up, made up of specialist experts. The role of the CESs in the work of the SDHI WG raises fundamental questions about the organisation of the expert appraisal. In this case, the feedback from the CESs was incorporated into the report by the WG coordination

team, either as comments or directly in the draft of the report. These comments and sometimes rewrites were subject to validation by all the WG experts *a posteriori*, which led to an excessive workload for the WG experts. This approach runs counter to the free choice of WG members as to whether and how to incorporate feedback from the rapporteurs in order to enhance the quality of the work.

While a broader look at the WG's output by the CESs is useful for clarifying its messages, it raises the question of how far this clarification can go without turning into a certain form of censorship or strategy of exhaustion. It also raises the question of what is the point of bringing together specialists in a subject if the views of non-specialists in that subject prevail as a basis for reporting.

End of the expert appraisal: loss of plurality of experts and organisational and time constraints

In November 2022, one of the experts left the WG. In December 2022, the CESs' feedback requesting very extensive modifications to the report affected the conduct of the expert appraisal. A new timetable with new meeting dates was drawn up. Two experts then voluntarily left the WG. As a result, the WG lost some of its plurality, since the resigning members were experts in mitochondrial diseases and metabolism, areas particularly targeted by the WG's internal request and particularly affected by the CESs' requested changes. It should be noted that in the meantime, one of the resigning members published some of the work they had conducted as part of the WG, some chapters of which no longer appear in the final report (doi: 10.3390/ijms24044045).

The obligation to quickly schedule new meeting dates was difficult to manage (the experts had other activities outside ANSES) and led to increased stress, pressure, workload and frustration for members who were unable to attend. As a result, decisions were taken without all opinions having been expressed, resulting in a loss of plurality and of the principle of adversarial debate, even when a quorum was present.

ANNEX 6: THE AGENCY'S ANALYSIS OF THE DISSENTING POSITION ON THE CONDUCT OF THE SDHI WG'S EXPERT APPRAISAL

I/ Background and purpose of the annex

During the expert appraisal following its internal request, ANSES recorded a dissenting position from a scientist in the SDHI Working Group (SDHI WG), relating to "the conduct of the expert appraisal". This dissenting position was shared with the entire SDHI WG before the conclusion of its work. Besides the author, it was supported by another expert from the SDHI WG. In view of the number of experts in the WG, it represented a minority position.

Given the title chosen by the author and what is questioned, ANSES decided not to include this minority position in the WG's report and annexes: it chose instead to append it to its opinion, relating to Section 2 on the organisation of the expert appraisal.

This annex documents the Agency's analysis of the points in this position relating to the expert appraisal methodology. Although it refers to the conclusions of the various groups involved in this expert appraisal, it does not provide any additional scientific analysis to that carried out in the expert appraisal.

II/ Role of the "organ toxicity" analysis in the collective expert appraisal

The Agency notes that the SDHI WG's report includes a Chapter 8 entitled " organ toxicity", which presents the analysis and conclusions adopted collectively by the WG following the work carried out. These conclusions are set out for each selected organ in the form of a box. It also notes that the WG's conclusion (Chapter 9) refers to this chapter in one of its paragraphs. In its own conclusion, the CES VSR states that the SDHI WG's choice of expert appraisal method "to identify possible common effects of SDHIs on certain organs, without being totally innovative, is original".

The fact that a summary and validated conclusions appear in the report is, in the Agency's view, a sign that the underlying work on organ toxicity has been summarised and exploited as part of the collective expert appraisal.

At the end of the report, and without constituting annexes as such, there are some personal contributions that served in particular as a basis for Chapter 8. The Agency notes the large volume of these personal contributions and that considerable time would have been needed for full collective validation. In this respect, it refers to the timetable for the expert appraisal mentioned in Section VII below. While it agrees with the author that it is unusual to include a sum of individual contributions in a collective expert appraisal report, the Agency decided to make them accessible.

With regard to the inclusion of the conclusions drawn by the SDHI WG from these contributions developing aspects of toxicity for each organ, which according to the author were "underrated", ANSES notes the disagreement of the CES VSR in using the results of the approach: "The CES VSR therefore disputes that such observations could be considered as effects, which reduces the relevance of a number of paragraphs in this chapter" (Section 3.2 of the opinion).

III/ Role of the analysis of toxicity reference values (TRVs) in the expert appraisal

The author of the minority opinion expressed regret in various ways that the work was mainly focused on the analysis of TRVs, which in her view constituted regulatory work.

The Agency refers to the terms of the internal request and the reminders in this opinion on the nature, role and method of determining such TRVs. Toxicity reference values are above all scientific – and not strictly regulatory – benchmarks resulting from a methodical analysis of the available knowledge on the toxicity of a substance. More broadly, ANSES refers to its methodological guide for developing TRVs (ANSES, 2017), which explains these analysis methods. The Agency's management added that it had intervened on several occasions at the request of the SDHI WG, to explain the meaning and objectives of the request, as well as that of the TRVs. As pointed out in the CES VSR's conclusions, determination of a TRV requires the consolidation of information observed in the available scientific data in order to constitute evidence of sufficient weight to be taken into account.

The Agency notes that the SDHI WG addressed the subject and expressed itself broadly in its conclusions, which included distancing itself from the values currently in force and determined in the past under the regulatory assessment processes for the substances in question.

IV/ Requests or choices regarding the hearings

In accordance with the fundamental principles of expert appraisal at ANSES (§10, and procedure R1[20], §6.1.2)[21], hearings are one of the tools available to help expert groups carry out their work when information or knowledge (scientific, field, etc.) is needed to supplement the data collected from the scientific literature or the dossiers compiled by applicants.

The decision to use them is taken by the group, in light of any problems identified in the progress of the expert appraisal, the anticipated contribution, and compatibility with the timetable (see point VII). Contrary to what was stated in the minority opinion, the hearings were not rejected by the coordination team, this was a collective decision by the appointed group of experts. The SDHI WG therefore decided to hold a hearing after a list of questions had been drawn up in order to examine a specific point of the expert appraisal in greater depth.

With regard to the author's request to interview a member of the ANSES Scientific Board who was involved in producing the report on "the credibility of scientific expert appraisals", the Agency refused this request for three reasons:

- The ANSES Scientific Board does not intervene in the scientific conduct of an expert appraisal process. Moreover, this request came at the end of the scheduled period, whereas the SDHI WG had decided on the expert appraisal method much earlier;
- It is an advisory body to the Agency, not to a working group or expert group;
- Lastly, the Scientific Board's opinion on the credibility of expert appraisals had already been made public by the Agency – and was therefore accessible – at the time the request was made.

[20] R1: quality procedure "producing a health-related expert appraisal", included in the ANSES quality system, under ISO 9001 certification
[21] https://www.anses.fr/fr/system/files/ANSES-Ft-PrincipesExpertise.pdf

V/ Epistemic blocks

The author of the minority position considers that the expert appraisal process contains an epistemic block resulting from the CES VSR's application of its methodological approach. In the Agency's view, the "de facto exclusion of certain diseases associated with SDHIs described in the literature" mentioned by the author does not constitute an exclusion of principle or method, but the application of its guidelines for setting reference values. This is a published and recognised reference standard (ANSES methodological guide, 2017). It also capitalises on the report by the Agency's Scientific Board on taking the weight of evidence and uncertainty into account in expert appraisal processes relating to substance hazards (ANSES Opinion, July 2016[22]). In particular, the existence of events identified in scientific studies is not ignored by this process, but is weighted to distinguish between non-recurring results and adverse effects of sufficient weight to be taken into account in setting health reference values.

VI/ Supervision of the CESs

As stated in ANSES's founding texts (CSP. L1313-1) and the framework memorandum on the collective expert appraisal methodology applied at ANSES[23], the conclusions of the Agency's collective expert appraisals are validated by the expert committees (CESs). These CESs are set up by decision of the Board of Administrators after consultation of the Agency's Scientific Board.

When a subject proves to be complex, and in application of its R1 expert appraisal procedure, ANSES may mandate a group of experts appointed *ad hoc* after a call for candidates to prepare the analysis and formulate proposed conclusions, under the aegis of one (or more) CESs.

As stipulated in the mandate signed by the Director General, the SDHI WG was set up and mandated in application of this framework, reporting to two CESs: the one on "Plant protection substances and products, biocontrol", given the nature and use of the substances examined, and the one on "Health reference values" (CES VSR), given the subject of the request.

The fact that a CES can intervene in a critical way on the adopted expert appraisal methodology or the results of a WG is part of the expert appraisal process. This almost invariably leads to joint conclusions after the CES's comments/observations/recommendations have been taken into account. These comments may lead to the reasoning behind the WG's conclusions being ranked or clarified, in order to arrive at conclusions on which there is complete agreement.

In the present case, the author of the minority position considered that these comments or observations were too numerous and not legitimate. Insofar as the central question of the expert appraisal was to re-examine the relevance of the TRVs in light of updated scientific knowledge on SDHIs and their mode of action, the Agency considers that the CES VSR had every right to comment on and question the WG on its scientific reasoning. This CES is responsible for proposing TRVs for a wide range of risk factors (not just chemicals but also fine particulate matter, for example) based on a variety of literature information (toxicological and epidemiological studies, data from regulatory dossiers), for all types of biological modes of action. The Agency also notes that following the discussion phase between the WG and the CES, the proposals to amend the TRVs were endorsed by both groups.

[22] ANSES OPINION and REPORT on the progress report on the assessment of the weight of evidence at ANSES: critical literature review and recommendations at the hazard identification stage
[23] https://www.anses.fr/fr/system/files/ANSES_note_cadrage.pdf

ANSES emphasises that it is particularly rare for a WG and the CES(s) to which it reports to disagree on their conclusions. Nevertheless, in accordance with the principles of transparency and the consideration of contradictory approaches, it confirms that the divergences on some of the WG's conclusions are reflected in the different paragraphs of its opinion and, regarding the minority positions, are available in full in the annex to the report.

VII/ The expert appraisal timetable and its impact on the process

The Agency pays close attention to the overall duration of the expert appraisal work. Its Committee for Ethical Standards & Prevention of Conflicts of Interest thus recommends ensuring that this period is limited. If the time commitment made by the experts when they applied is significantly exceeded, this may lead some of them to leave the group.

With this expert appraisal, the initial period scheduled for the SDHI WG was 12 months. On several occasions, the WG's chair, speaking on behalf of the experts, asked the Agency to extend the mandate in view of the scale of the task and the time needed to start work on determining the expert appraisal approach. ANSES therefore extended the SDHI WG's mandate three times, while mentioning the high level of external expectations regarding the finalisation of the expert appraisal.

Without prejudging the reasons – inherently specific to each person – that led some experts to leave the SDHI WG, three resignations were noted. One of the resigning experts told the Agency that the reason for this was a disagreement with the approach adopted for the expert appraisal. It should be noted that the information provided by these experts prior to their resignation was incorporated into the finalised and validated report.

ANSES had set the end of May 2023 as the deadline for completing the work of the SDHI WG so that the CESs to which it reported could have access to it. As with many expert appraisals, the final phases required additional meetings, in agreement with the SDHI WG, to validate the text (formulation of the report and, in particular, its conclusions) within the time remaining. The large size of the report also had an impact on the validation process.

VIII/ Conclusion

After analysing the various points raised in the minority position, which the Agency notes was adopted by two of the SDHI WG experts, ANSES did not identify any shortcomings or practices that failed to follow the fundamental principles of expert appraisal that it implements and applies through its work processes, in order to uphold the values of independence, transparency, adversarial debate and scientific plurality.