EUROPEAN CHEMICALS AGENCY

Helsinki, 12 August 2020

Addressees
Registrants of JS_36888-99-0_Isoind listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
13/11/2014

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 5,5'-(1H-isoindole-1,3(2H)-diylidene)dibarbituric acid
EC number: 253-256-2
CAS number: 36888-99-0

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadlines provided.

A. Requirements applicable to all the Registrants subject to Annex VIII of REACH

1. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) with the Substance;

2. Justification for an adaptation of a Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.) based on the study requested under Section B.1; with the Substance;

B. Requirements applicable to all the Registrants subject to Annex IX of REACH

1. Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.; test method OECD TG 413) in rats with the Substance. The study must include measurements of lung burden and bronchoalveolar lavage fluid (BALF) analysis as described in the current version (25 June 2018) of the test guideline;

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method OECD TG 414) in a first species (rat or rabbit), oral route with the Substance.

C. Requirements applicable to all the Registrants subject to Annex X of REACH

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method OECD TG 414) in a second species (rat or rabbit), oral route with the Substance.

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Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.
To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annexes VII and VIII of REACH, if you have registered a substance at 10-100 tpa;
- you have to comply with the requirements of Annexes VII, VIII and IX of REACH, if you have registered a substance at 100-1000 tpa;
- you have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

Registrants are only required to share the costs of information that they must submit to fulfil the information requirements for their registration.

The Appendix on general considerations addresses issues relevant for several requests while the other Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in points A.2 and B.1 above in an updated registration dossier by ***20 May 2022***, and the information requested in points A.1, B.2 and C.1 above by ***22 May 2023***.

You must also update the chemical safety report, where relevant, including any changes to classification and labelling based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix on general considerations

(i) Assessment of the Grouping of substances and read-across approach, in light of the requirements of Annex XI, Section 1.5.

You seek to adapt the following standard information requirements by applying (a) read-across approach(es) in accordance with Annex XI, Section 1.5:

- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)

ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following appendices.

Grouping of substances and read-across approach

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (addressed under 'Predictions for toxicological properties').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[2] and related documents[3, 4].

A. Predictions for toxicological properties

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies).[5]

You have provided studies conducted with a substance (Pigment Yellow 185, EC number 278-388-8) other than your Substance in order to comply with the REACH information requirements. You have not provided documentation as to why this information is relevant for your Substance and for the endpoints assessed in this decision.

In the absence of a read-across justification documentation, ECHA cannot verify that the properties of your Substance can be predicted from the data on the source substance(s).

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[2] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9

[3] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[4] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

[5] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.6.1

In an attachment to your comments to the initial draft decision you provide results of static solubility and dissolution kinetics studies performed with 14 different pigments. ECHA notes that the study reports included in your comments do not contain any studies performed with the Substance. No justification for the relevance of the substances used in those studies is provided, and no read-across hypothesis is included. Based on this limited amount of information it is not possible to make any conclusions on the relevance of the provided studies. It is at your discretion to generate and provide the necessary supporting information in order to justify your adaptation.

In a second attachment to your comments to the initial draft decision you indicate that based on health surveillance examinations, adverse health effects suspected to be related to several pigment exposure have not been observed among workers. ECHA notes that although no adverse health effects have been observed in occupational health surveillance examinations, this information does not show proof of lack of exposure.

B. Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

Appendix A: Reasons for the requests to comply with Annex VIII of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 10 to 100 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII and VIII to REACH.

1. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

An *In vitro* cytogenicity study in mammalian cells or an *In vitro* micronucleus study is a standard information requirement in Annex VIII to REACH.

You have provided an adaptation according to Column 2 of Annex VIII, Section 8.4.2. (first indent) in your dossier by providing an *in vivo* study performed according to OECD TG 474 (2008) with the Substance.

In addition, you have provided an *in vitro* study (OECD TG 473, 1997) with an analogue substance.

We have assessed this information and identified the following issue(s):

In vivo OECD TG 474 study

To fulfil the adaptation according to Column 2 of Annex VIII, Section 8.4.2. (first indent), the study must qualify as "*adequate data from an in vivo cytogenicity test*". The *in vivo* study must be either a micronucleus test or a chromosomal aberration test, performed according to OECD TG 474 or 475, respectively[6].

To be considered adequate, the *in vivo* study you submitted has to meet the requirements of OECD TG 474. These parameters include proof that the substance has reached, or may have reached, the bone marrow[7].

The reported data on the *in vivo* study you submitted did not include a verification of systemic or target tissue (bone marrow) exposure to the Substance. Specifically, the data provided do not show that there is a statistically significant decrease in the PCE/NCE ratio. No information to conclude on bioavailability is provided either. Without this information it is not possible to know whether the testing material reached the bone marrow.

Therefore, considering the uncertainties on the test material reaching the bone marrow or not, the provided *in vivo* test is not adequate, and the column 2 adaptation is rejected.

OECD TG 473 (in vitro cytogenicity) study with an analogue substance

In addition, you have also adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

As explained in the Appendix on general considerations your adaptation is rejected.

Based on the above, the information you provided does not fulfil the information requirement.

[6] ECHA Guidance R.7a, Table R.7.7-3, p.558
[7] ECHA Guidance R.7a, Section R.7.7.6.3.

To fulfil the information requirement for the Substance, both the *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) and the *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered suitable.

2. Justification for an adaptation of the Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)

A Short-term repeated dose toxicity study (28 days) is a standard information requirement in Annex VIII to REACH. This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII or a general adaptation rule under Annex XI.

You have provided one 28-day repeated dose toxicity study according to OECD TG 407 ([redacted] 2000) performed with an analogue substance.

We have assessed this information and identified the following issue(s):

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

As explained in the Appendix on general considerations your adaptation is rejected. Therefore, the information requirement is not fulfilled.

Column 2 of Annex VIII, Section 8.6.1., provides that an experimental study for this endpoint is not needed if a reliable sub-chronic (90 days) or chronic toxicity study is available.

The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see Section B.1). According to Column 2 of Annex VIII, Section 8.6.1., and to prevent unnecessary animal testing, a short term toxicity study (28 days) does not therefore need to be conducted.

Because you still must comply with the information requirement in Annex VIII, Section 8.6.1., you are requested to submit a justification for the adaptation provided in Column 2 of that provision.

Appendix B: Reasons for the requests to comply with Annex IX of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII to IX to REACH.

1. Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.)

A Sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX to REACH.

You have provided an adaptation according to Column 2 of Annex IX, Section 8.6.2. in your dossier stating that the substance is unreactive and no adverse effects were observed in the subacute oral toxicity study.

We have assessed this information and identified the following issue(s):

As provided in Annex IX, Section 8.6.2, Column 2, you may adapt the information requirement, provided you fulfil all the following criteria, including:

(i) the Substance is not inhalable and
(ii) there is no evidence of absorption, and
(iii) no evidence of toxicity in a 28-day 'limit test',
(iv) particularly if such a pattern is coupled with limited human exposure.

You provided the following justification: *"In accordance with column 2 of EC regulation 1907/2006, testing of subchronic toxicity is not indicated if the substance is unreactive and no adverse effects were observed in the subacute oral toxicity study. In this case, the substance showed no indication of toxicity in the OECD 421 study and the analogue showed no toxic effects in a 28-day repeated dose toxicity study (OECD 407) at 1000 mg/kg bw. As discussed in the section of toxicokinetics, the substance is considered to be too insoluble for transport across biological membranes. Therefore, no testing of subchronic toxicity is considered necessary".*

In your comments on the initial draft decision you:

- include results of static solubility and dissolution kinetics studies performed with 14 different pigments;
- indicate that based on health surveillance examinations, adverse health effects suspected to be related to several pigment exposure have not been observed among workers.

You have not demonstrated that any of the criteria are met:

(i) The data provided in your dossier indicate that the Substance is inhalable (as discussed further below) and uses are reported that include spray application.
(ii) You did not demonstrate that there is no evidence of absorption. No studies investigating toxicokinetic properties such as absorption were included in the dossier. ECHA notes that the study reports included in your comments on the initial draft decision do not contain any studies performed with the Substance. No justification for the relevance of the substances used in those studies is provided, and no read-across hypothesis is included. Based on this limited amount of information it is not possible to make any conclusions on the relevance of the provided studies.

It is at your discretion to generate and provide the necessary supporting information in order to justify your adaptation. If you do so, you are responsible for demonstrating the fulfilment of the requirements of Annex IX, Section 8.6.2, Column 2.

(iii) The submitted toxicity study (OECD TG 407) was performed with an analogue substance. As explained under Appendix General considerations, your adaptation according to Annex XI, Section 1.5 is rejected. Therefore the study cannot be used to demonstrate that there is no evidence of toxicity. Additionally, the referred OECD TG 421 study is not providing relevant information for this endpoint.

(iv) Human exposure cannot be considered as limited because widespread uses (e.g. PROCs 7 and 11), including professional and consumer uses are reported. Regarding your comment, ECHA notes that although no adverse health effects have been observed in occupational health surveillance examinations, this information does not show proof of lack of exposure and does not support your adaptations.

Therefore, your adaptation is rejected.

Based on the above, the information you provided does not fulfil the information requirement.

Following the criteria provided in Annex IX, Section 8.6.2, Column 2, the inhalation route is the most appropriate route of administration to investigate repeated dose toxicity[8].

The sub-chronic toxicity study must be performed according to the OECD TG 413, in rats and with administration of the Substance by inhalation.

The information provided in the technical dossier and the chemical safety report on properties of the Substance and its uses (industrial, professional and consumer uses; including industrial and non-industrial spraying) indicate that human exposure to the Substance by the inhalation route is likely. More specifically, the Substance is reported to occur as a dust with a significant proportion of particles of inhalable size. Furthermore, the Substance is respirable (4.5% < 10 µm), of low water solubility and consequently there is a potential for accumulation of the substance in the lungs.

There is evidence that the lower respiratory tract is the primary site of deposition and retention of the Substance, because it is poorly soluble in water and respirable. Therefore, you are requested to perform measurements of lung burden and bronchoalveolar lavage fluid (BALF) which are specifically designed to address such situation. The latest guidance on how to perform such measurements are described in the revised version of the OECD 413 test guideline (paragraphs 50-51) adopted on 25 June 2018.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.

You have adapted the information requirement according to Column 2 of Annex IX, Section 8.7. stating that the substance is not toxic and is not absorbed.

In addition, you have provided a Screening for reproductive/developmental toxicity study (OECD TG 421, [redacted] 2013) performed with the Substance.

[8] ECHA Guidance R.7a, Section R.7.5.4.3.

We have assessed this information and identified the following issue(s):

Annex IX column 2 adaptation not met

According to Annex IX, Section 8.7., Column 2, third indent, the study does not need to be conducted if the substance is of low toxicological activity. This needs to be demonstrated with three concomitant criteria, two of them being:
(i) that it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure; and
(ii) that there is no or no significant human exposure.

You justified the adaptation by stating that the Substance is of low toxicological activity, there is no systemic toxicity, no systemic uptake and no significant human exposure. However, you have not demonstrated that all criteria are met:
(i) You have not provided any toxicokinetic data to prove that no systemic absorption occurs. The OECD TG 421 study and OECD TG 407 study provided in the dossier did not investigate toxicokinetic properties such as absorption.
(ii) Furthermore, as discussed under section 1 of Appendix C, the reported uses of the Substance indicate that there is a possibility of significant human exposure. (e.g. PROCs 7 and 11).

Therefore, your adaptation is rejected.

OECD TG 421 study does not fulfill the requirement

In order to be considered compliant and enable assessing if the Substance is a developmental toxicant, the information provided has to meet the requirements of OECD TG 414 in one species. These parameters include information on structural malformations and variations.

In the study you have provided, structural malformations and variations are not investigated as required in the PNDT study (OECD TG 414).

Therefore, the provided information does not fulfil the information requirement.

A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species with oral[9] administration of the Substance.

[9] ECHA Guidance R.7a, Section R.7.6.2.3.2.

Appendix C: Reasons for the requests to comply with Annex X of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier at a tonnage abve 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to REACH.

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is a standard information requirement under Annex X to REACH.

In order to be compliant and enable concluding if the Substance is a developmental toxicant, the information provided has to meet the requirements of OECD TG 414 in two species.

You have adapted the information requirement according to Column 2 of Annex IX, Section 8.7. based on lack of toxicity and absorption, and no significant human exposure of the general population. As explained in section C.2. above, your adaptation is rejected and the information requirement is not fulfilled.

A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species with oral[10] administration of the Substance.

[10] ECHA Guidance R.7a, Section R.7.6.2.3.2.

Appendix D: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

The compliance check was initiated on 25 March 2019.

ECHA notified you of the draft decision and invited you to provide comments

ECHA took into account your comments and did not amend the requests.

Included in your comments, you outlined various aspects that do not directly affect the decision making process of this draft decision, thus ECHA has dealt with it in separate communications.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

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Appendix E: Observations and technical guidance

1. The information requirement under Section 8.7.3. of Annex X to REACH (Extended one-generation reproductive toxicity study, EOGRTS) is not addressed in this decision, because the information from the Sub-chronic toxicity study (90-day), requested in the present this decision, is relevant for the design of the EOGRTS.

2. This compliance check decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

3. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

4. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries'[11].

5. Test material

   Selection of the test material

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/ impurity.

   Technical reporting of the test material

   The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values and other parameters relevant for the property to be tested. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

[11] https://echa.europa.eu/practical-guides

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[12].

6. List of references of the ECHA Guidance and other guidance/ reference documents[13]

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[14]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents[15]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.

[12] https://echa.europa.eu/manuals
[13] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[14] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[15] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

AppendixF: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.