Decision number: CCH-D-0000002676-67-03/F Helsinki, 7 June 2013

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For 2-[(2-methoxy-4-nitrophenyl)azo]-N-(2-methoxyphenyl)-3-oxobutyramide, CAS No 6358-31-2 (EC No. 228-768-4), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration dossier for 2-[(2-methoxy-4-nitrophenyl)azo]-N-(2-methoxyphenyl)-3-oxobutyramide, CAS No 6358-31-2 (EC No 228-768-4), referred to as Pigment Yellow 74 in the dossier and the text below, submitted by [redacted] (Registrant).

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates after 8 March 2013, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

The compliance check was initiated on 6 June 2011.

On 24 April 2012 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

On 24 May 2012 ECHA received comments from the Registrant to ECHA's draft decision. On 19 June 2012 the Registrant updated his registration dossier.

ECHA considered the Registrant's comments received and the updated registration dossier and amended the draft decision by removing the request for representative microscopy images from an appropriate method, and information on the size of the aggregate/agglomerate particles.

On 8 March 2013 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, Competent Authorities of the Member States did not propose amendments to the draft decision and ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

This compliance check decision does not prevent ECHA to initiate further compliance checks on the present dossier at a later stage.

II. Information required

Pursuant to Articles 41(1)(a), 41(3), 10(a)(vii) and 3(28), as well as Annex VII of the REACH Regulation the Registrant shall submit information in the form of complete robust study summaries for the registered substance for the following endpoint:

- Granulometry (Annex VII, 7.14.).

More specifically, the Registrant is requested to submit the following information on the granulometry of the registered substance:

- The particle size distribution of primary particles of the registered substance according to the following methods:
  - Transmission Electron Microscopy (TEM), and
  - Scanning Electron Microscopy (SEM)

  The particle size distributions shall be reported both on a mass and particle number basis
- A detailed description of the experimental method(s) used. This shall include the sample selection, sample preparation, description of the measurement, statistics, as specified in Section III below. The information shall be reported in accordance with the prescriptions provided in Section III below. In any case, the information submitted shall enable an independent assessment of the results;
- Expected percentage change of reported values in the future (e.g. variations between production batches).

Taking into consideration the data currently available in the dossier, Section III below specifies all the test methods that ECHA considers appropriate in order to determine the particle size distribution of primary particles of the registered substance.

Based on the dossier and in the absence of suitable information, ECHA cannot be in a position to determine precisely the information that is actually required to characterise the specific forms of a substance. Only the Registrant of the substance knows the relevant forms of that substance and is therefore able to determine the particle size distribution of primary particles. Based on this knowledge, he may consider that a method requested by ECHA or the information required are not suitable and necessary in order to determine the particle size distribution of the specific form(s) of the substance. Based on his knowledge, the Registrant may also consider that the particle size distribution of primary particle can be better determined by a method which he has himself designed. In any case where the Registrant would deviate from the methods imposed by the present decision and the information it requires, it is the Registrant's exclusive responsibility 1) to ensure that ECHA is in a position to determine the particle size distribution of primary particles the substance and 2) to justify the reasons for which the test methods imposed by the present or the information requested in the present decision may have been omitted.

Therefore, if the Registrant eventually decides to submit only part of the information specified in Section III and if the submitted information does not enable ECHA to determine the particle size distribution of primary particles of the substance, the registration will not be considered to cover the forms containing primary particles which have not been properly determined.

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated IUCLID dossier to ECHA by **9 December 2013**.

III. Statement of reasons

Section 7.14. of Annex VII of the REACH Regulation requires the Registrant to provide information on the granulometry of the registered substance as manufactured in the industrial processing method used by the Registrant.

To ensure a high level of protection of human health and the environment, the REACH Regulation imposes the determination of hazards and risk irrespective of the form of the substances concerned. This includes more specifically nanoforms of substances, which may trigger specific hazardous properties and risks, as already highlighted by various institutions, including the European Parliament.[1]

In fact, the current scientific knowledge establishes that the risks of nanoforms of substances are likely and significant. Indeed, the specific risks of nanoforms are not founded on mere hypotheses that have not been scientifically confirmed. These risks have actually been fully demonstrated by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR).[2] The fact that there is still some degree of scientific uncertainty as to the existence or extent of such risks does not, by itself, discharge registrants from characterising nanoforms in order to carry out their duties under the REACH Regulation. Based on the above, the Registrant is compelled to scientifically assess the potentially adverse effects of nanoforms.

Furthermore, it is self-evident that in order to determine the hazardous properties and the appropriate risk management measures for substances in different forms, it is necessary to characterise the substance in terms of its physical form, in particular regarding nanoforms, before determining the corresponding hazards and assessing the exposure of humans and the environment and the associated risk management measures. The characterisation of nanoforms of the substance is a pre-requisite to the determination of all the hazardous properties and appropriate risk management measures concerning the registered substance. Therefore, it is essential that suitable granulometry information is submitted, especially in order to identify precisely whether the registered substance includes nanoform(s).

In that respect, an explicit definition has been provided in the Commission Recommendation on the definition of nanomaterial:

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[1] "*Whereas nanomaterials [...] potentially present significant new risks due to their minute size, such as increased reactivity and mobility, possibly leading to increased toxicity in combination with unrestricted access to the human body, and possibly involving quite different mechanisms of interference with the physiology of human and environmental species*". Recital D of European Parliament Resolution of 24 April 2009 on Regulatory aspects of nanomaterials.

[2] "*There is sufficient evidence that there can be a change in some properties of the material at the nanoscale which is, for instance, due to the increase in surface-to-volume ratio. These nanospecific properties raise concerns over their potential to cause harm to humans and the environment. The chemical reactivity of nanoparticles often relates to the surface area. Consequently, the chemical reactivity per mass dose increases for smaller particles of the same type. This effect may or may not be associated with an increase in biological activity or toxicity*". SCENIHR, Opinion of 8 December 2010 on *Scientific Basis for the Definition of the Term «nanomaterial »*, page 31.

"Nanomaterial' means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm-100 nm."

"Agglomerated or aggregated particles may exhibit the same properties as the unbound particles. Moreover, there can be cases during the life-cycle of a nanomaterial where the particles are released from the agglomerates or aggregates. The definition in this Recommendation should therefore also include particles in agglomerates or aggregates whenever the constituent particles are in the size range 1 nm-100 nm".[3]

ECHA notes that the constituent particles referred to in the Recommendation are primary particles, and the particle size reported shall refer to primary particle size and not to the aggregate or agglomerate.

In addition, the determination of the granulometry information necessary to establish the potential adverse effects of nanomaterials has been further specified in OECD guidance on sample preparation and dosimetry for the safety testing of manufactured nanomaterials:

"values for particle size, shape, size distribution and degree of agglomeration will depend both on the employed methodology as well as on the properties of the medium supporting the sample under consideration".[4]

"dosimetry should always report mass concentration, but for nanomaterials, the results may be better expressed as a function of surface area or particle number because particle size and specific area may play a major role in determining the toxicity of nanomaterials".[5]

ECHA notes that the registration contains inadequate information for establishing the granulometry of the registered substance. In the dossier with submission number [redacted], which was the basis of ECHA's initial draft decision, the Registrant stated the following in the Overall Remarks field in Section 4.5 of the IUCLID dossier:

"In case of using intensive shear forces and adding surface active substances and/or solvents (e.g. as a preparation for transmission electron microscopy) agglomerates and/or aggregates can be visualised which may contain primary particles smaller than 100 nm."

Following ECHA's draft decision, the Registrant updated the dossier to remove the above statement. Instead, the updated technical dossier contains three endpoint study records on granulometry, which are discussed below.

1) The key study supplied is done using a laser diffraction method, performed using ISO standard 13320-1. The updated dossier included additional details on the test method applied and on the results. This updated information partially addressed the request in ECHA's initial draft decision. However, the information in the updated dossier as well as the Registrant's comments on the draft decision clearly indicate that the particle size data provided is a volumetric based distribution for the aggregated/agglomerated particles. Therefore this study does not provide adequate

[3] Commission Recommendation on the Definition of nanomaterials of 20 October 2011, 2011/696/EU.
[4] OECD "Preliminary guidance notes on sample preparation and dosimetry for the safety testing of manufactured nanomaterials" of 31 May 2010, Section A.1.1 page 25.
[5] *Idem.*, Section III, page 18

information on the number sized distribution of the primary particles of the registered substance.

2) A non-key study performed using TEM, which includes attached TEM images. The images are of aggregated and/or agglomerated particles. However, the study does not provide any information on the primary particle size distribution of the substance.

3) A non-key study providing information on the BET surface area of the registered substance, showing that the surface are is 33.1 m^2/g. However, this information is not sufficient to establish the primary particle size distribution of the substance, nor is it sufficient to show if the substance is a nanomaterial according to the Commission Recommendation on the definition of nanomaterial. The Commission Recommendation on the definition of nanomaterial considers that a material falls under the definition if the specific area **by volume** is greater than $60m^2/cm^3$. Converting the specific area by mass to a volume specific surface area is possible using a substance's density. The density of this substance is 1.43 g/cm^3 according to the information provided in the IUCLID dossier, which gives a volume specific surface area of 47.3 g/cm^3. However, this calculation assumes that the density of the bulk material is the same as that of the nanomaterial/nanoform of the substance. However, the density of the bulk material may differ from that of the nanomaterial, and the Registrant has not given information on the density of the nanoform of this substance.

In addition, the Registrant provided additional information in his comments on ECHA's draft decision. In his comments the Registrant states that the measurements provided in the dossier have been performed on the substance as delivered from the production plant, and that this measurement reflects the normal situation at worker's/downstream users sites when handling the material. Furthermore, the Registrant states that the results of the laser diffraction study show that the powder contains no unbound (primary) particles. In addition, while TEM imaging of the substance reveals that it consists of primary particles with a size of <100 nm, these primary particles are observed only when the substance is treated (e.g. using solvents and/or shear forces), and are not present in the non-pretreated substance as produced and sold, and do not reflect the situation when handling the substance *per se*.

ECHA takes note of the Registrant's comments. However, ECHA considers that the determination of the particle size distribution of primary particles of the registered substance is essential to enable the identification of hazards and risks posed by the substance irrespective of its form.

Firstly, ECHA notes that the Commission Recommendation on the definition of nanomaterials refers to particles in either an unbound state, or in aggregates or agglomerates. Therefore the primary particle size distribution is relevant regardless of the aggregation/agglomeration of the particle. Given that the substance appears to contain primary particles in the 1-100 nm range, it is necessary to obtain information on the size distribution of these primary particles in order to fulfill the information requirement for the endpoint on granulometry. Whether workers and/or downstream users are exposed to these primary particles is a separate issue, which is relevant for other parts of the dossier, such as the performance of the exposure assessment (if needed). ECHA notes that the dossier itself does not contain an exposure assessment, nor does it contain information on the identified uses of the substance. Therefore it is not possible to verify if indeed the Registrant's dossier covers such uses where primary particles may be dispersed.

Secondly, according to the SCENIHR, physico-chemical properties such as particle size, particle size distribution and surface properties are key parameters to understand the potential toxic effects of nanomaterials:

> *"Depending on the nanomaterial, the majority of the particulates may actually be agglomerates/aggregates. This may lead to the misinterpretation that agglomerates/aggregates of nanoparticles that have dimensions well beyond the 100 nm size are not considered nanomaterials. Yet they retain specific physicochemical properties which are characteristic for nanomaterials, most likely due to their relative large specific surface area (SSA). Therefore, when describing a nanomaterial it is important to describe not only the mean particle size but also the size of the primary particles. In addition, information on the presence of agglomerates/aggregates should be presented. When the mean particle size deviates (i.e. is larger) from the primary particle size this would indicate the presence of agglomerates/aggregates".*[6]

Based on the above, the adequate characterisation of a substance requires the submission of information determining the particle size distribution of primary particles of that substance.

The Registrant noted in his comments that there are currently no harmonized procedures for the measurement of primary particle size distribution of nanomaterials. However, while there are currently no standardized protocols (e.g. OECD Guidelines) available to determine the primary particle size distribution by number, this in itself does not prevent the Registrant from providing information on this endpoint. ECHA notes that for the analytical methods required to characterize substances (e.g. NMR spectroscopy, mass spectroscopy, HPLC, GC) ECHA does not provide standard protocols that can be applied to each registered substance, as these protocols need to be tailored to the individual substance in question. The same applies in relation to the methods concerned by the present decision.

Furthermore, the Registrant indicated that they are currently participating in a joint project with the Joint Research Center (JRC-Ispra) to develop methods to measure the primary particle size of nanomaterials. Therefore the Registrant requested ECHA to postpone the request for information on primary particle size.

ECHA took this request into account but acknowledges that this project, which was supposed to be finalised by July 2012, has not been completed as of the the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation. ECHA also notes that the Registrant did not update the dossier with any results, even intermediary, of this work. In fact, the Registrant has not provided any relevant information justifying why the project is a requisite for the Registrant in order to execute the present Decision.

In addition, ECHA notes that the on-going nature of this project does not prevent the Registrant to already determine the particle size distribution of primary particles of the substance based on the analytical methods requested by the present Decision. Indeed, publicly available company literature such as brochures and technical data sheets does already report the average primary particle size of various organic pigments such as the registered substance.[7] This information indicates that the registered substance has primary

[6] SCENIHR, opinion of 19 January 2009 on Risk Assessment of Products of Nanotechnologies, page 7.
[7] http://www.pigments.clariant.com/bu/pigments/PDS_Pigments.nsf/www/DS-OSTS-7SHD9H?open
http://www.clas.clariant.com/C125702E0040AEE5/vwLookupDownloads/CLAS_TS_106_1e.pdf/$FILE/CLAS_TS_106_1e.pdf

particles in the size range of 1-100 nm, and that it is possible to measure the number based primary particle size distribution using the methods specified in the present decision.

It is nevertheless recognized that it is possible that one single method is not capable of measuring particle size distributions of all size ranges of a substance.[8] Therefore, several methods may be required in order to determine the different particle sizes of a same substance.

In addition, ECHA recognises that the measurement of particle size and particle size distribution is inherently method dependent. Indeed, any reported particle size distribution should be reported in the context of the method used to measure the particle size or size distribution, and not as an absolute value. Nevertheless, any measurement used by the Registrant in order to fulfil this information requirement needs to fulfil certain criteria. First, the measurement needs to be able to distinguish between primary particles on one hand, and aggregates and agglomerates on the other. Second, the measurement must be able to provide a number based particle size distribution as the final output.

Based on these two criteria, and the available information on the registered substance, ECHA can determine which methods are appropriate for the measurement of the primary particle size distribution in relation to that specific substance. Given that the substance is aggregated/agglomerated, it is clear that ensemble methods such as DLS, such as that provided by the Registrant in his dossier, are not appropriate for the measurement of primary particle size distribution of this substance. This is because such methods are incapable of distinguishing between primary particles and aggregates/agglomerates. Second, since the particles are non-spherical and appear to be polydisperse, such ensemble methods cannot reliably provide a number based particle size distribution, because these methods rely on mathematical calculations to convert their output into a number based particle size distribution, and these calculations assume a spherical particle shape. This assumption has clearly been nullified for these particles.

Therefore, based on the information in the dossier, ECHA concludes that electron microscopy (EM) is the only appropriate method that can be used to measure the primary particle size distribution of these substances. Given the method dependence of primary particle size measurement, ECHA requires the Registrant to provide the primary particle size distribution using the two following methods:

1) Transmission Electron Microscopy (TEM): TEM is an appropriate method for the determination of primary particle size of these pigments, as it is capable of measuring particles down to 1 nanometer, can be used to distinguish visually between aggregates, agglomerates, and primary particles, and can provide a number based particle sized distribution.

2) Scanning Electron Microscopy (SEM): SEM is also an appropriate method for the determination of primary particle size of these pigments, since like TEM, it is capable of distinguishing between aggregates, agglomerates, and primary particles, and can provide a number based particle size distribution.

If the registration covers multiple forms of the same substance, the difference in forms of the registered substance does not relieve the Registrant from complying with the obligation to identify accurately all hazards posed by the substance, irrespective of the forms. As a result and based on his knowledge of the substance, the Registrant may consider necessary

[8] ECHA Guidance on Information Requirements R.7a, of May 2008, section R.7.1.14.2, page 143.

to characterize all the forms of in order to be able, eventually, to determine their specific hazards. In principle, this requires the Registrant to test with the required methods all these different forms. Alternatively, the Registrant may decide to test only one or some of these forms. This approach may fulfil the information requirement only if the Registrant would justify scientifically why he considers a particular form to be representative of other forms of the registered substance and would document that this choice would not lead to an underestimation of the hazards.

As already explained above, in relation to analytical methods required to characterize substances, such as TEM and SEM, such methods need to be tailored to the specific substance being tested.

When performing the required methods, the Registrant shall provide sufficient details to allow for the method to be reproduced and allow for an independent assessment of the applied method and the resulting information. In addition, the Registrant is responsible to ensure that the sample selection and preparation gives a result that is representative for the registered substance. ISO standard 14488:2007 gives instructions for the sampling and sample splitting of particulate materials for the purpose of determining particle properties.

As a minimum, the Registrant is required to provide the following details in their updated IUCLID dossier:

- Sample selection
  The Registrant shall ensure that the sample selected is representative for the test substance. The Registrant shall therefore include a detailed description of how the test material was selected, including any subsampling necessary from the bulk powder.
- Sample preparation
  The Registrant shall submit as detailed as possible information on sample preparation. This shall include at least complete information on sample dispersion, and more particularly:
    - what physical forces/shear forces were used including stirring and sonication (the type of sonication; probe sonication or bath sonication, time and intensity of sonication used); and
    - the use of solvents/dispersing agents necessary to disperse the sample (including identity of the solvent/dispersing agent); and
    - the concentration of the sample.

  If the particles are not dispersed well enough in order to distinguish the primary particles, the results of the tests might not be considered valid.
- Description of the measurement
  The Registrant shall submit a detailed description of:
    - the instrument used; and
    - measurement conditions; and
    - magnifications used; and
    - whether manual or automatic counting was used; and
    - the use of any sputter coating, if needed.

- Statistics
  The Registrant shall specify in the dossier:
  - the number of images used; and
  - the number of particles counted.

The information reported shall allow for an independent evaluation of the results of the study, and shall fulfil the definition of a robust study summary as described in Article 3(27) of the REACH regulation. This shall include as a minimum:

- the median and mean primary particle size; and
- the particle size distribution; and
- a histogram of the primary particle size distribution.

In any case, the information required must be provided in accordance with the Commission Recommendation on the definition of nanomaterial mentioned above.

The Registrant shall clearly differentiate between agglomerates, aggregates and primary particles for all particle sizes reported in Section 4.5 of the IUCLID dossier.

Regarding how to report the granulometry of the registered substance in IUCLID, the Registrant shall report the information required above in IUCLID Section 4.5. Further technical details on how to report, in general, granulometry in IUCLID are available in sections 4.4.5 of the Data Submission Manual 5 on the ECHA website.[9]

IV. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

[redacted]
Jukka Malm
Director of Regulatory Affairs

[9] http://echa.europa.eu/documents/10162/13653/dsm5_tech_dossier_manual_v2-8_en.pdf