EUROPEAN CHEMICALS AGENCY

Helsinki, 31 May 2016

Addressee [redacted]

Decision number: CCH-D-2114330559-45-01/F
Substance name: Potassium 1,2-bis(2-ethylhexyloxycarbonyl)ethanesulphonate
EC number: 231-308-5
CAS number: 7491-09-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 25.04.2012
Registered tonnage band: 100-1000T

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA requests you to submit information on

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2; test method: EU B.26/OECD TG 408) in rats with the registered substance**

2. **In vivo mammalian erythrocyte micronucleus test (Annex IX, Section 8.4, column 2; test method: OECD TG 474) in mice or rats, oral route[1]**
   or
   in vivo mammalian bone marrow chromosomal aberration test (Annex IX, Section 8.4, column 2; test method: OECD TG 475) in mice or rats, oral route [2]
   or
   in vivo mammalian alkaline comet assay (Annex IX, Section 8.4, column 2; test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum/jejunum; with the registered substance[2]

3. **Identification of DNEL(s) and risk characterisation (Annex I, Section 1.4. and 6.): revise long-term DNEL(s) for workers and for the general population, inhalation, dermal, oral route for systemic effects using the assessment factors recommended by ECHA and revise the risk characterisation accordingly *or* provide a detailed justification for not using the recommendations of ECHA Guidance R.8 for DNEL derivation**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by 07 December 2017. You shall also update the chemical safety report, where relevant.

[1] Only the OECD TG is mentioned since it has recently been updated while the corresponding EU test method has not yet been updated.
[2] Only the OECD TG is mentioned since it has recently been adopted and the corresponding EU test method has not yet been published.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

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, shall 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[3] by Guilhem de Seze, Head of Unit, Evaluation E1

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

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Appendix 1: Reasons

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

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

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier you have provided results for repeated dose toxicity (90-day) from a study conducted with the analogue substance sodium 1,2-bis(2-ethylhexyl-oxycarbonyl)ethanesulphonate (oral.002 [redacted]).

ECHA agrees that the sodium salt of 1,2-bis(2-ethylhexyl-oxycarbonyl)-ethanesulphonate may be used to provide the standard information on repeated dose toxicity for the potassium salt of 1,2-bis(2-ethylhexyl-oxycarbonyl)-ethanesulphonate using a read-across approach because, after dissociation, both substances result in the same organic anion and the cations sodium and potassium do not need to be considered.

However, the study oral.002 does not provide the information required by Annex IX, Section 8.6.2., because it does not meet the requirements of Annex XI, Section 1.1.2 and Annex XI, Section 1.5.

The study is from 1969 and was not conducted according to the requirements of the current OECD test guideline 408 and GLP. Annex XI, Section 1.1.2 (2) and Annex XI, Section 1.5 require for non-GLP studies and studies used for read-across purposes adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test method referred to in Article 13(3). The study provided has been conducted using oral administration via the diet with one dose (1 % of test substance) instead of at least three doses as required in OECD 408. One dose might only be sufficient, if a limit test with 1000 mg/kg bw/day is performed. In this case, the dose was 750 mg/kg bw/day. The study does not contain a functional observation battery. Clinical chemistry parameters investigated did not cover the current range of parameters and were investigated in only 5 animals per sex instead of 10. Also haematology parameters were investigated in 5 animals per sex. In conclusion, ECHA considers that these key requirements are not covered and, therefore, that the requirements of Annex XI, Section 1.1.2 (2) and Annex XI, Section 1.5 are not met.

Furthermore, Annex XI, Section 1.1.2 (2) and (3) and Annex XI, Section 1.5 require for non-GLP studies and studies used for read-across purposes "*reliable coverage*" and "*reliable documentation*", respectively. The study was conducted by Industrial Bio-Test Laboratories. ECHA notes that irregularities in the conduct of safety studies were detected for this laboratory in 1976 resulting in court proceedings. Afterwards, the US Environmental Protection Agency concluded in a report of 1983 (Summary of the IBT review) that 76 % of a sample of reports that they investigated were invalid. Under these circumstances, there are legitimate suspicions that the laboratory tampered with the results of the studies conducted before 1976 and that these studies are, therefore, unreliable.

You did not provide any evidence that for the study on the analogue substance sodium 1,2-bis(2-ethylhexyl-oxycarbonyl)ethanesulphonate (oral.002) the results should nevertheless be considered as reliable. Without proper documentation addressing this concern, ECHA has to regard the study results as not reliable. ECHA therefore considers this report as not meeting the provisions in Annex XI, Section 1.1.2 (2) and (3) and Annex XI, Section 1.5.

You have also provided supporting information for the information requirement sub-chronic toxicity study (90 day). In the study oral.003 [redacted] various read-across substances were tested in parallel to the identified analogue substance (the sodium salt). However, Annex XI, Section 1.5 also requires a justification on why and how these substances can be used to predict the sub-chronic toxicity (90 day) for the registered substance. Nevertheless, no such justification is given. Furthermore, the study must be rejected on the same grounds as oral.002 [redacted], because it was conducted according to the same protocol and with the same flaws by the same laboratory. Therefore the study also does not meet the requirements of Annex XI, Section 1.1.2.

Finally, the supporting studies oral.004, oral.005, oral.006, oral.007 are studies from 1943 in rats, monkeys, rabbits and dogs with a Klimisch rating of 4 (not assignable). However, REACH Annex XI, Section 1.1.2 requires "*adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3)*". The investigated parameters in the provided studies are not covering the key parameters investigated in an OECD 408 study, such as clear identification of test material, organ weights, histopathology, clinical chemistry and neurobehavioural tests, and the reporting does not allow ECHA to come to independent conclusions.

Another study with Klimisch rating 4 investigated according to the title danthron, dioctyl sodium sulfosuccinate, poloxalkol and combinations in chronic dog toxicity studies. It is not clear what was tested and how in this study. In conclusion, the submitted supporting studies do not provide the information required by Annex IX, Section 8.6.2., because they do not meet the requirements of Annex XI, Section 1.1.2 and Annex XI, Section 1.5.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and most specifically because the substance is a solid, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, July 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration.

According to the test method EU B.26/OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

In your comments to the draft decision you addressed some of the issues listed above. ECHA considered these and points out the following:

i. oral.002 [redacted]. You acknowledge that there might be a principle issue with the "reliable coverage" and "reliable documentation" of the study, since it was conducted by Industrial Bio-Test Laboratories (IBT) during a time when there was evidence of scientific fraud by this test laboratory. You state that you will provide an audit report which concludes that the results accurately reflect the raw data. ECHA notes that this particular IBT study has not been audited by the EPA / FDA post-hoc programme.
   Moreover, the OECD Manual for Investigation of HPV Chemicals in Chapter 3

(agreements reached up to December 2005) recommends caution in accepting studies from IBT not audited by the EPA / FDA post-hoc programme (http://www.oecd.org/chemicalsafety/risk-assessment/49191960.pdf). The study has been audited by a consultant and according to your statement the auditor concludes also: "serious deficiencies remain in the IBT report which cannot be corrected from the raw data available". Currently ECHA cannot assess what the deficiencies are which the auditor is referring to. Irrespective of the possibility to address the IBT quality issue sufficiently, ECHA considers that the concern provided above about the shortcomings of the study in comparison with a modern guideline study remain and that the key requirements are not covered and, therefore, that the requirements of Annex XI, Section 1.1.2 (2) and Annex XI, Section 1.5 are not met.

ii. oral.007. You state that additional information is available for the dog study and that the study year 1943 is indicated wrongly in the IUCLID file. Currently, ECHA regards the results of this study as not reliable. Therefore they cannot be used to support conclusions on the registered substance. For the use of results from sodium dioctyl sulfosuccinate, which appears to be the tested substance in the dog study, you intend to provide a document justifying why such results can be used as source studies to predict results for the registered substance.

ECHA concludes that currently such information is not in the dossier and cannot be assessed. The request for the sub-chronic toxicity study (90-day) therefore remains in the decision.

You are reminded that this decision does not take into account any updates submitted after 27 October 2015. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: EU B.26/OECD TG 408) in rats.

2. In vivo mammalian erythrocyte micronucleus test or in vivo mammalian bone marrow chromosomal aberration test or in vivo mammalian alkaline comet assay (Annex IX, Section 8.4, column 2)

Mutagenicity is an information requirement as laid down in Annex VIII, Section 8.4 of the REACH Regulation. Column 2 of Annex IX, Section 8.4 provides that "*If there is a positive result in any of the in vitro genotoxicity studies in Annex VII or VIII and there are no results available from an in vivo study already, an appropriate in vivo somatic cell genotoxicity study shall be proposed by the Registrant*".

A. Read-across to sodium 1,2-bis(2-ethylhexyl-oxycarbonyl) ethanesulphonate

The analogue substance sodium 1,2-bis(2-ethylhexyl-oxycarbonyl)ethanesulphonate did not induce mutations in the Ames test up to concentrations close to toxic range, both with/without liver metabolic activation (S9) system.

The technical dossier contains also an *in vitro* cytogenetics study in V79 CHO cells (*in vitro*.003 [redacted]) performed according to OECG TG 473 and GLP with the analogue substance sodium 1,2-bis(2-ethylhexyl-oxycarbonyl)-ethanesulphonate. ECHA agrees that the sodium salt of 1,2-bis(2-ethylhexyl-oxycarbonyl)-ethanesulphonate may be used to provide the standard information on chromosamal aberration studies *in vitro* for the potassium salt of 1,2-bis(2-ethylhexyl-oxycarbonyl)-ethanesulphonate using a read-across approach. However ECHA disagrees with the interpretation of the results. You consider the results of this study as ambiguous, whereas ECHA considers the results as positive on the basis of the provided information (IUCLID section 7.6.1).

The evaluation criteria against which the results were evaluated as positive were:

1) Statistically significant increases in the proportion of cells with structural aberrations (excluding gaps) occurred at one or more concentrations;
2) The proportion of aberrant cells at such data points exceeded the normal range;
3) The results were confirmed in the second experiment.

On the basis of the available information (IUCLID section 7.6.1) ECHA concludes that the criteria are met. Cultures treated with sodium dioctyl sulphosuccinate in the presence of S-9 in Experiment 1 had significantly increased frequencies of cells with aberrations at the highest dose level chosen for analysis (120 µg/ml). Numbers of aberrant cells in both replicates receiving this concentration fell outside the historical negative control range. Two attempts to reproduce this result were made. In the second attempt small, statistically significant increase in cells with aberrations were seen at both 125 and 130 µg/ml. Numbers of aberrant cells fell outside the normal range in only a single replicate at the highest dose.

You argue that the results are, nevertheless, ambigous. Your reasoning (in the IUCLID file and the CSR) is:

a) There were problems to achieve 50-75% mitotic inhibition;
b) The effect of the repeat experiments was considered to be of marginal biological significance because numbers of aberrant cells fell outside the normal range in only a single replicate at the highest dose;
c) Marginal reductions in mitotic activity occurred with increasing concentration until a threshold was reached at which point cell division ceased. The fact that chromosome aberrations were only clearly seen at a dose very close to this toxic threshold implies that the mechanism of induction was probably via an indirect rather than direct mechanism, that is, involved a target other than DNA;
d) The marginal increase in chromosome aberrations was observed in CHO cells in the presence of S9 only.

ECHA notes that no supporting evidence is provided for these arguments.

Further, the fact that a positive response is only observed in the presence of S-9 mix, is an intentional part of the study design to detect substances which need metabolic activation to act as a mutagen. Selecting doses close to the threshold of toxicity is also part of the study design. The fact that the replicate experiment showed again a positive response has to be taken as a confirmation of the first experiment and cannot be classified as of marginal significance. Tabular data allowing ECHA to verify the claim that cytotoxicity may be causative for the effects are not provided. Also the historical control data are not provided. Therefore ECHA considers that the results indicate that the substance is inducing chromosomal aberrations under the conditions of the test.

B. Read-across to sodium dihexylsulfosuccinate

You also provided another *in vitro* chromosome aberration study (OECD 473, 2006 V79 cells, in vitro.005 Cognis CO600014-3) conducted with sodium dihexylsulfosuccinate, which did not show increases in frequencies of chromosomal aberrations. ECHA notes that this substance has another chemical structure than the registered substance and will not result in the same anion compared to the registered substance when dissociated. You did not explain why and how this substance can be used to predict the chromosomal aberration results with the registered substance and how this result would be regarded as overwriting the result with the proposed analogue substance sodium 1,2-bis(2-ethylhexyl-oxycarbonyl)ethanesulphonate substance.

Since there is no documentation for the attempted prediction provided, ECHA cannot assess the read-across justification and does not consider the read-across to be a reliable basis to predict the properties of the registered substance. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, ECHA rejects this adaptations in the technical dossier that is based on Annex XI, Section 1.5. The result of this test is, therefore, not considered suitable to address the concern triggered by the test with the analogue substance sodium 1,2-bis(2-ethylhexyl-oxycarbonyl)ethanesulphonate.

According to the ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.7.6.3 (July 2015), the mammalian erythrocyte micronucleus test ("MN test", OECD TG 474), the mammalian bone marrow chromosomal aberration test ("CA test", OECD TG 475) or the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) are suitable to follow-up a positive *in vitro* result on chromosomal aberration if the test substance or its metabolite(s) will reach the target tissue.

According to the test method (OECD TG 474 / OECD TG 475), the test shall be performed in mice or rats. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s), performance of the test by the oral route is appropriate.

According to the test method (OECD TG 489), the test shall be performed in rats. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s), performance of the test by the oral route is appropriate. The test shall be performed by analysing tissues from liver as primary site of xenobiotic metabolism and glandular stomach and duodenum/jejunum as sites of direct contact. In view of several expected or possible variables (different tissue structure and function of the glandular stomach and the duodenum/jejunum; different pH conditions; variable physico-chemical properties and fate of the substance; probable different absorption rates of the substance and its possible breakdown product(s) between these two tissues), ECHA considers that it is necessary to increase the reliability of the analysis of genotoxicity at the site of contact by sampling both tissues.

In your comments to the draft decision you addressed some of the issues listed above. ECHA considered these and points out the following:

i. In vitro genotoxicity.003. You acknowledge that more details have to be provided to support your conclusions with regard to interpretation of the study and you intend to provide such information.
ii. In vitro genotoxicity.004. You intend to provide a read-across document to justify the use of this study as a source study to predict the results for the registered substance. Furthermore you intend to provide results from another study conducted with sodium 1,4-diisotridecyl sulphonatosuccinate.

ECHA concludes that currently such information in not in the dossier and cannot be assessed. The request for a clarification of the chromosamal aberration in vivo remains in the decision.

You are reminded that this decision does not take into account any updates submitted after 27 October 2015. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vivo* mammalian erythrocyte micronucleus test (test method: OECD TG 474) in mice or rats, oral route, or *in vivo* mammalian bone marrow chromosomal aberration test (test method: OECD TG 475) in mice or rats, oral route, or *in vivo* mammalian alkaline comet assay (test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum/jejunum.

Reminders

According to paragraph 10 of the OECD TG 474 (Mammalian Erythrocyte Micronucleus Test, updated on 26 Sept 2014) or paragraph 6 of the OECD TG 475 (Mammalian Bone Marrow Chromosomal Aberration Test, updated on 26 Sept 2014), "*If there is evidence that the test substance(s), or its metabolite(s), will not reach the target tissue, it may not be appropriate to use this test*". Additionally, according to paragraph 48 (d) of the OECD TG 474 or paragraph 44 (d) of the OECD TG 475, a test chemical is considered clearly negative if "*Bone marrow exposure to the test substance(s) occurred*". Accordingly, if a substance is negative in this test, and if it is not possible to demonstrate that bone marrow exposure to the substance occurred, then ECHA will consider any remaining uncertainty concerning the mutagenic potential of the substance and whether to request any further information.

You are reminded that according to Annex IX/X, Section 8.4, column 2 of the REACH Regulation, if positive results from an *in vivo* somatic cell study are available, "*the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered*". In case you decide to perform the micronucleus/chromosomal aberration assay, you may consider making a testing proposal to conduct the mammalian spermatogonial chromosome aberration test (OECD TG 483) whenever the results of the somatic *in vivo* genotoxicity tests indicate that chromosomal aberrations occurred. In case you decide to perform the comet assay, you may consider examining gonadal cells, as it would optimise the use of animals. ECHA notes that a positive result in whole gonads is not necessarily reflective of germ cell damage since gonads contain a mixture of somatic and germ cells. However, such positive result would indicate that the substance and/or its metabolite(s) have reached the gonads and caused genotoxic effects. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

3. Identification of DNEL(s) and risk characterisation (Annex I, Sections 1.4. and 6.): revise long-term DNEL(s) for workers and for the general population, inhalation, dermal, oral route for systemic effects using the assessment factors recommended by ECHA and revise the risk characterisation accordingly *or* provide a detailed justification for not using the recommendations of ECHA Guidance R.8 for DNEL derivation

Pursuant to Articles 10(b) and 14(1) of the REACH Regulation, the registration shall contain a chemical safety report which shall document the chemical safety assessment conducted in accordance with Article 14(2) to (7) and with Annex I of the REACH Regulation.

Annex I, Section 1.4.1 of the REACH Regulation requires that the following factors shall, among others, be taken into account when deriving DNELs:

a) the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;
b) the nature and severity of the effect;
c) the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies; and
d) that the DNELs reflect the likely route(s), duration and frequency of exposure.

The ECHA Guidance on information requirements and chemical safety assessment Volume 8, Chapter R.8 [1] provides further details and specifically provides default factors which should be applied to derive DNELs in the absence of substance specific information and may be adapted based on substance specific justification.

The assessment factors (AF) that you applied to the starting point (NOAEL in a 90-day study) are not in line with the default factors listed in the ECHA guidance.

First, the assessment factor for the remaining differences in the interspecies differences (factor 2.5) has not been used.

Second, the assessment factor for the intraspecies differences for the general population has been reduced from 10 to 7.

No substance specific justification has been provided for these two deviations from the default values. A mere reference to a general ECETOC publication is not regarded by ECHA as a substance specific justification.

Third, you argue that a factor of 2 is not needed in this specific case for the oral route to inhalation route extrapolation. Your argument does not provide substance-specific information on differences in uptake at oral and inhalation exposure but uses an argument on exposure likelihood, which is not relevant for DNEL derivation. Furthermore, you use the particle size as an argument to conclude that the exposure likelihood is low. ECHA notes that information on the particle size (i.e. granulometry information) is not available in the dossier to support such argument and it is not relevant for the DNEL derivation anyhow. Furthermore the substance is produced and marketed in a solvent, so aerosol exposure, and not dust exposure, appears to be the exposure type of concern.

Outcome

You are requested to revise the long term DNELs for workers and for the general population using the assessment factors recommended by ECHA and re-assess the related risks or to provide a full justification for not using the recommended assessment factors in DNEL derivation (Annex I, Section 1.4.1).

ECHA notes that the starting point currently used for the DNEL derivation is not regarded as valid (90-day study with RA substance regarded as not reliable) and a new 90-day study repeated dose toxicity study according to OECD 408 in the rat is requested in this decision. Consequently, the starting point to derive the long term DNELs shall be reviewed when the results of the new study are available.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 17 September 2015.

ECHA notified you of the draft decision and invited you to provide comments. ECHA took into account your comments, which were sent within the commenting period, and they are reflected in the Reasons (Appendix 1).

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

ECHA invited you to comment on the proposed amendments. You did not provide comments on the proposed amendments within the deadline set.

ECHA considered the proposed changes and modified the draft decision.

ECHA referred the draft decision to the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-47 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

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

3. In carrying out the tests required by the present decision it is important to ensure that the particular sample of substance tested is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured. If the registration of the substance covers different grades, the sample used for the new test(s) must be suitable to assess these. Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the tests to be assessed.