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Application of ring study: Water toxicity determinations by bioluminescence assay with *Vibrio fischeri*

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Abstract

Acceptance of toxicity bioassays as effective analytical tools in environmental areas needs guarantees of standardization but also validation. Ten European laboratories took part in an inter-laboratory study using different commercial devices based on bioluminescence inhibition of bacteria *Vibrio fischeri*. Reproducibility and stability by short toxicity endpoints, effective concentration that gives 10%, 50% and 80% of inhibition (EC_{10}, EC_{50} and EC_{80}) is evaluated. Parametric and non-parametric statistic is applied and performance of participant laboratories is addressed by z-scores calculated by non-parametric statistic. z-Score classification was based on harmonised protocol for proficiency testing of analytical laboratories (satisfactory $|z| \leq 2$; questionable $2 < |z| \leq 3$; unsatisfactory $|z| > 3$). Tested samples were phenol, 3,5-dichlorophenol and influent wastewater. Based on z-score classification, more than 70% of the laboratories showed a satisfactory performance for phenol, 3,5-dichlorophenol and influent wastewater (86%, 90% and 70%, respectively). Reproducibility and stability was observed in toxicant references and in wastewater samples. EC_{80} determination appears to be more robust that EC_{10} and EC_{50}. EC determinations can be considered favorable at 5 and 15 min of exposition, in particular for EC_{80}. The use of different commercial devices can not be considered an additional source of variation.

Keywords: *Vibrio fischeri*; Inter-laboratory; Toxicity; Environment; Water analysis

1. Introduction

Integrated strategy with biological and chemical analysis for water quality control is a recognized complementary approach [1–3]. Chemical analysis has limitations related to the inability to evaluate the bioavailability of contaminants or to foresee interactive effects of pollutants in complex water matrices. In this sense, bioassays are becoming popular analytical tools to assess potential risk linked with the presence of chemicals (e.g. pesticides, disinfection by-products, pharmaceuticals, hormones) in waters.

Among ecotoxicity tests, bioluminescent inhibition test using bacteria *Vibrio fischeri* has been widely applied in water analysis and extensive database on pure chemicals is available [4–9]. Comparative studies with other toxicity bioassays, such as *Daphnia magna* test or fish tests, have been also conducted to establish correlations with *V. fischeri* assay because they can respond with different sensitivity to toxicants [1,6,10–12]. Toxicological profile of toxicants is better understood when the effects are determined by different organisms that represent different trophic levels and the use of a battery of bioassays is usually recommended for assessing environmental impact [3,6,11].

On the other hand, the acceptance of a toxicity test as effective analytical tool requires guarantees of standardization but also validation. In spite of *V. fischeri* assay is considered such as one of the toxicity tests more widely applied and which experimental procedure has been adapted for official standards in several countries [13–16], factors linked to experimental procedure (e.g. sample preparation, sample composition) or to bacteria (e.g. conservation, reconstitution, time to equilibration to test temperature) can be potential causes of variability for toxicity results [17]. In this sense, the utility and validity of *V. fischeri* assay to assess toxic effects of chemicals or wastewaters is conditional on consistency of results. Participation in inter-laboratory studies is a recommended practice to ensure quality assurance as

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well as measurement consistency, but inter-laboratory exercises concerning *V. fischeri* assay are scarce in literature [17,18,19].

This work presents results of a ring study performed between 10 European laboratories. Phenol, 3,5-dichlorophenol and influent wastewater were tested by different commercial devices based on bioluminescence inhibition assay with *V. fischeri*. Reproducibility was based in short toxicity endpoints (5 and 15 min of exposition), determined by effective concentration (EC) that gives 10%, 50% and 80% of inhibition (EC_{10}, EC_{50} and EC_{80}). For that, parametric and non-parametric statistic was applied and performance of participant laboratories was addressed by z-scores calculated by non-parametric statistic. z-Score classification was based on harmonised protocol [20] for proficiency testing of analytical laboratories (satisfactory $|z| \leq 2$; questionable $2 < |z| \leq 3$; unsatisfactory $|z| > 3$).

2. Experimental

2.1. Standards and wastewater samples

Two reference toxicants (phenol, 3,5-dichlorophenol) and influent wastewater samples were selected in this inter-laboratory study. Six series of samples (batches) were distributed in polyethylene containers, among the participant laboratories to evaluate the reproducibility and sample stability along the time (5 months). Samples were preserved at −20 °C and processed by adjustment of pH in a range of 6–8 (using HCl or NaOH) and adjustment of osmotic pressure to 2% NaCl.

Solutions of phenol and 3,5-dichlorophenol were prepared at concentration of 60 and 50 mg L^{-1}, respectively, by a central source to minimize sources of variation not associated with the laboratories. Phenol and 3,5-dichlorophenol were included in this inter-laboratory study as usual toxicant references selected in several publications and protocols such as in Microtox® test [19–21,22].

Influent wastewater sample was also selected to be tested because degradation process can occurs along the time changing the toxicity results. The influent wastewater samples were collected from a sewage wastewater treatment plant (STP) that receives wastewaters from an industrialized area. Previously to its distribution, wastewater samples were processed also by central source by centrifugation and filtration.

2.2. V. fischeri toxicity test: commercial devices

The participant laboratories used reagent (*V. fischeri* NRRL-B 11177) from different commercial devices: Microtox® (Azur Environmental, Carlsbad, CA), Toxalert® (Merck, Darmstadt, Germany), BioFix® Lumi (Macherey-Nagel, Düren, Germany), ToxTracer® (Skalar, Breda, The Netherlands). Preparation and reconstitution of reagent were carried out according with the device protocols. Samples were analyzed on duplicate by luminometers. The concentrations tested for each sample were: 45.45%, 22.73%, 11.36%, 5.68% and 2.84%. Dilution of samples was performed using 2% NaCl solution and pH of samples was also checked to be in optimal range (6–8) for toxicity analysis. The percent of inhibitory effect (%) was determined by comparing the response given by a saline control solution (2% NaCl) that corresponding to the diluted sample. Effective concentration (EC) values (EC_{10}, EC_{50}, EC_{80}) were derived after plotting percentage inhibition against concentration. Toxicity measurements were determined at 5 and 15 min of exposition.

2.3. Statistical treatment of results

At the close of inter-laboratory exercise, results were processed to assess reproducibility and sample stability along 5 months. Mean, standard deviation of the mean (S.D.), median and median absolute deviation (MAD) values were determined in accordance with generally accepted laboratory statistical procedure. Quality indicator z-score proposed by IUPAC was calculated with the formula (1) [23]:

$$z\text{-score} = (x - \mu)/\text{MAD} \quad (1)$$

where x is the median result of participant laboratories (assigned value, an estimate for the "true value"), μ the result of each laboratory for this test (laboratory measured value) and MAD that were calculated by the median of absolute deviations of each test result and the median. z-Score classification was based on harmonised protocol for proficiency testing of analytical laboratories (satisfactory $|z| \leq 2$; questionable $2 < |z| \leq 3$; unsatisfactory $|z| > 3$) [20].

3. Results and discussion

3.1. Phenol

Phenol has been commonly used as reference toxicant in *V. fischeri* test because of its stability and reproducibility of toxicity measurements [19–21,22]. For statistical treatment, results were organized in data set of laboratories, batch of samples and toxicity measurements (EC_{10}, EC_{50} and EC_{80}). A representation of mean and median values corresponding to toxicity determinations (EC_{10}, EC_{50} and EC_{80}) at 5 and 15 min is given in Fig. 1. Standard deviation (S.D.) of mean and median absolute deviation (MAD) are also showed in Fig. 1. Mean EC values are higher than median EC values and in only one case, mean and median were equal (EC_{50} at 5 min). The mean is different than the median because it treats all data equally including more data at the extreme lower values than extreme higher values. S.D. and MAD were higher for EC_{10} than EC_{50} and EC_{80} determinations.

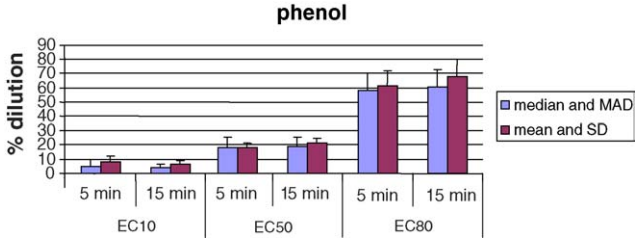

Fig. 1. Mean, median, standard deviation (S.D.) and median absolute deviation (MAD) of EC_{10}, EC_{50} and EC_{80} at 5 and 15 min of exposition corresponding to toxicity data of phenol (mean and median, $n = 10$ of the mean and median of batches, $n = 6$ reported by 10 laboratories).

Variability in measurement to detect low percent of inhibition such as 10% is usually expected. Measurement at 50% of inhibition also showed similar S.D. and MAD and was higher than EC_{80} measurements. On the other hand, S.D. and MAD for EC_{50} determination at 5 min of exposition are higher than the obtained at 15 min as well as for EC_{10} determination. For EC_{80}, S.D. and MAD are similar for measurements at 5 and 15 min and appear to be more robust than EC_{10} or EC_{50} determinations.

The data set was also evaluated using z-scores applying median rather than mean due to median is more robust towards outliers and mean was more sensitive to extreme lower values. Advantages to use median rather than mean are particularly useful if a ring exercise has a limited data set. As well as, the uncertainty of median is easy to calculate, assuming that the measurements are independent. This is generally a reasonable assumption in these types of tests, when there are not a large number of results from one particular laboratory or from all laboratories [25]. Therefore, data set of laboratories, batch of samples and toxicity measurements (EC_{10}, EC_{50} and EC_{80}) were treated applying z-scores calculated by median and MAD.

In Fig. 2a and b, z-scores for laboratories and batches related to EC_{50} for phenol at 5 min (Fig. 2a) and 15 min (Fig. 2b) are illustrated. Dotted lines in Fig. 2a and b show z-score classification to evaluate the performance of laboratories in terms of reproducibility and stability. A significant number of laboratories achieved satisfactory performance for bacthes during 5 months. More than 67% of laboratories showed z-scores within ±1 and when allowing z-score of ±2, the number of satisfactory performing laboratories increased to more than 76%. Slight differences can be observed when z-scores for laboratories and batches at 5 and 15 min are compared. In fact, for 5 min of exposition, more than 80% of the results showed z-score ±2, while 76% of the results were also satisfactory for determinations at 15 min. There was not found a significant variation among laboratories that applied different commercial devices. Thus the use of different commercial devices does not appear to be an additional source of variation. On the other hand, the results of laboratories with codes lab 7, 9, 10 and for batches 1, 4 and 5 were unsatisfactory with positive z-score values >3. Negative z-score values <3, indicating also unsatisfactory results were observed for lab 2, 11, 4, 8 and for batches 1, 2, 4 and 6.

Fig. 2c and d compile z-score values for laboratories and EC_{10}, EC_{50} and EC_{80} values for phenol at 5 min (Fig. 2c) and 15 min (Fig. 2d). Most of laboratories (86–90%) also achieved a satisfactory performance. Contrary unsatisfactory performance related with EC_{50} was observed for labs 11, 2 (z-score values <2) and labs 7, 9 (z-score values >2). When z-scores within ±1 was considered, 66% of the results were in this range for EC_{10}, EC_{50} and EC_{80} at 15 min while 46% of them were observed at 5 min.

As alternative approach to assess data, criteria based on "fitness for purpose" (FFP) assuming 30% error was also applied

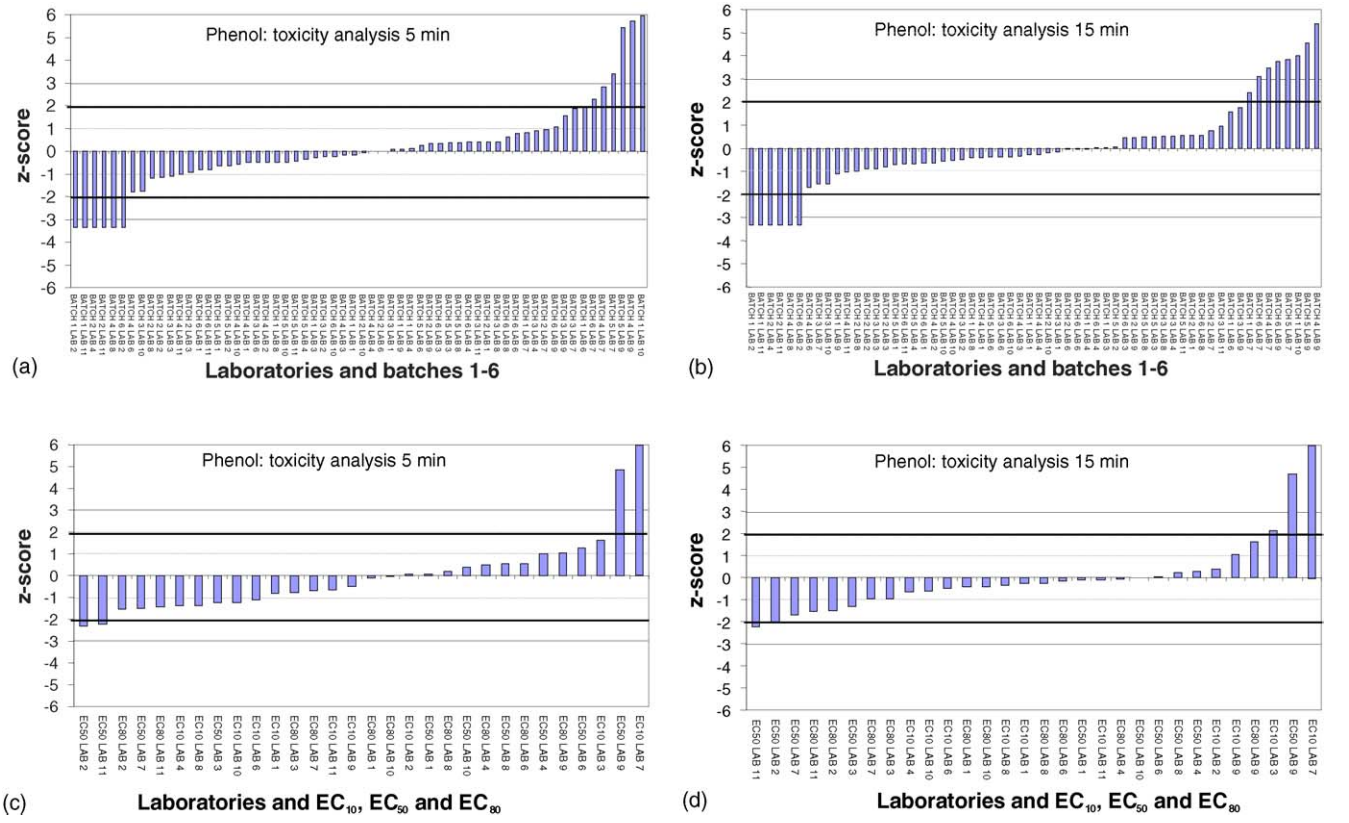

Fig. 2. Display of z-scores values for participant laboratories corresponding to toxicity analysis of phenol. (a) z-Score values for laboratories and batches related to EC_{50} at 5 min of exposition; (b) z-score values for laboratories and batches related to EC_{50} at 15 min of exposition; (c) z-score values for laboratories and EC_{10}, EC_{50}, EC_{80} values at 5 min of exposition (median of six batches); (d) z-score values for laboratories and EC_{10}, EC_{50}, EC_{80} values, at 15 min of exposition (median of six batches). Dotted lines show the z-score classification (satisfactory ($|z| \leq 2$), questionable ($2 < |z| \leq 3$), unsatisfactory ($|z| > 3$)).

as acceptable dispersion of values and more than 93% of results were considered to be into this margin. This is a common practice in most proficiency testing schemes in analytical chemistry where the use of scoring system is recommended in the harmonised protocol to helps the participant assess the accuracy of their results [26,20].

3.2. 3,5-Dichlorophenol

3,5-Dichlorophenol is also a compound commonly tested in *V. fischeri* test as toxicant reference. Dose-response curves of phenol and 3,5-dichlorophenol are showed in Fig. 3a where EC_{50} at 15 min, is calculated from percent of inhibition (%) against concentration. 3,5-Dichlorophenol showed lower effective concentration ($EC_{50,15\,min}$ = 4.1 mg/L) than phenol ($EC_{50,15\,min}$ = 10.4 mg/L).

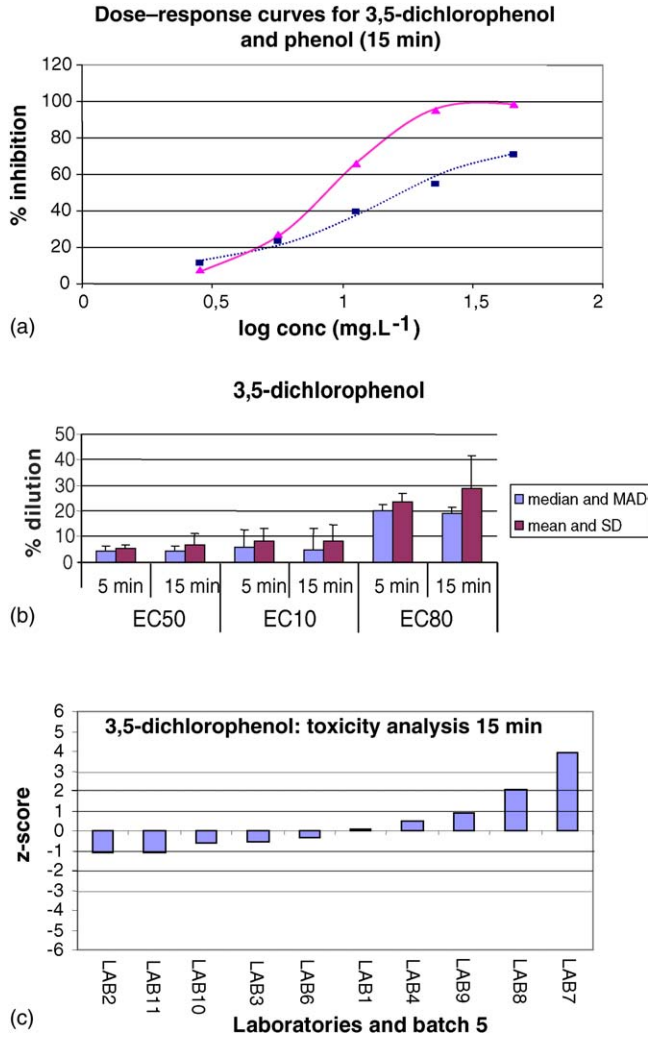

Fig. 3. (a) Dose response curves for phenol (■) and 3,5-dichlorophenol (▲) at 15 min of exposition; (b) mean, median, S.D. and MAD of EC_{10}, EC_{50} and EC_{80} at 5 and 15 min, for 3,5-dichlorophenol (mean and median, n = 10 of the mean and median of batches, n = 6 reported by 10 laboratories); (c) z-score values for 3,5-dichlorophenol obtained from laboratories (n = 10) corresponding to batch 5 (toxicity analysis at 15 min). Dotted lines show z-score classification (satisfactory ($|z| \leq 2$), questionable ($2 < |z| \leq 3$), unsatisfactory ($|z| > 3$)).

Mean, median, S.D. and MAD corresponding to analysis at 5 and 15 min are showed in Fig. 3b. Similarly to phenol, for 3,5-dichlorophenol, mean EC values were also higher than median values. Close median EC values were observed in particular for EC_{50} and EC_{10} at 5 and 15 min. Contrary to phenol, S.D. and MAD in EC_{50} were observed to be higher than in EC_{10} at 5 and 15 min. However, EC_{80} results to be also more robust than EC_{10} and EC_{50}. But in the case of mean for EC_{80} at 15 min, S.D. was significant greater, supporting the use of median rather than mean.

Data set were also evaluated considering batch of samples and EC_{10}, EC_{50} and EC_{80} values at 5 and 15 min, for each laboratory. The results obtained show in general a good reproducibility of data reported by the laboratories related to the evaluation of laboratories and batches as well as laboratories and EC_{10}, EC_{50} and EC_{80} values. Most of the results (90%) showed z-scores within ±2 in both data sets and for the tested times of exposition (5 and 15 min). As example, Fig. 3c shows z-score values for laboratories and batch 5, where only the lab with code 7 had a z-score value >2. The results obtained testing 3,5-dichlorophenol also support the stability in the time and that the use of different commercial devices can not represent cause of variation.

3.3. Influent wastewater

For controlling wastewater quality, in addition to chemical analysis based on global parameters (e.g. chemical oxygen demand, COD; biochemical oxygen demand, BOD) actually, toxicity tests has a potential application in conventional wastewater treatment plants (WWPTs) to assess biological effects on different organisms. In this sense, there is a need of support the use toxicity tests and influent wastewaters have been also included for validation studies in this inter-laboratory exercise. The presence of colour or turbidity can be interferences leading to erroneous results. Suspended particles can disperse or adsorb light causing turbidity, which can affect toxicity measurements. Thus, particles in water that adsorb light can be interferences by adsorbing the light produced by the bacteria. In this way, a reduction in the light intensity can be measured that is not due to the toxicity of the sample.

However, tests based on bioluminescence organisms have not a correction procedure that can attenuate interferences observed for samples containing optically absorbing particles. In spite that, the previous processing based in centrifugation and filtra-

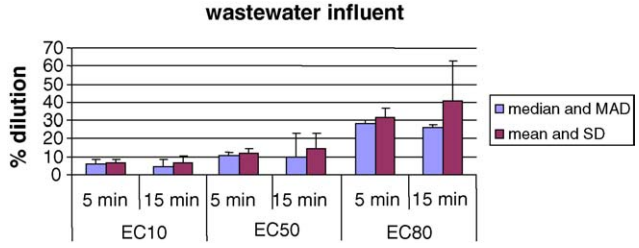

Fig. 4. Mean, median, S.D. and MAD of EC_{10}, EC_{50} and EC_{80} at 5 and 15 min of exposition for influent wastewater (mean and median, n = 10 of the mean and median of batches, n = 6 reported by 10 laboratories).

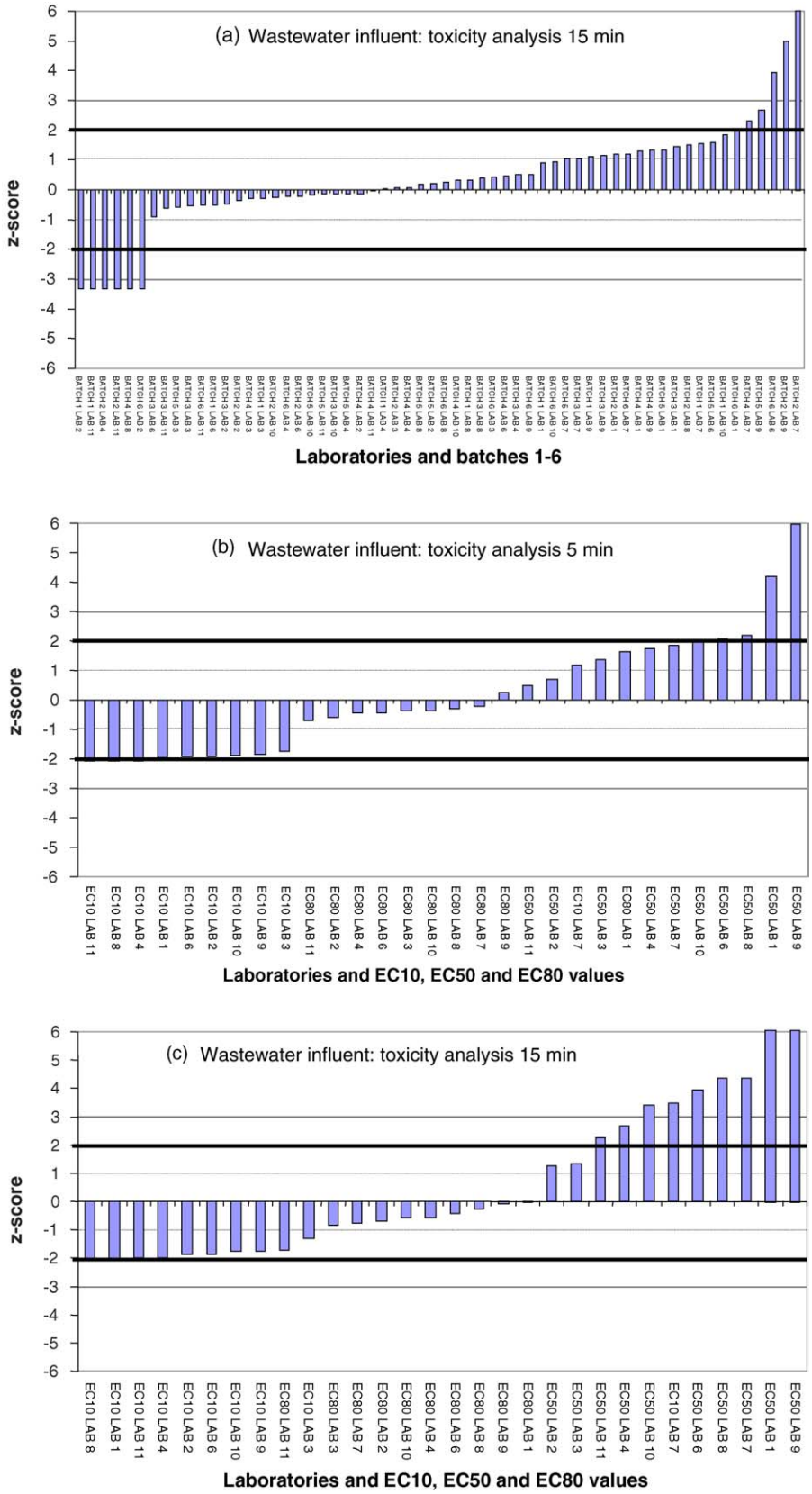

Fig. 5. Display of z-scores values for laboratories corresponding to toxicity analysis of phenol. (a) z-Score values for laboratories and batches related to EC_{50} at 15 min of exposition; (b) z-score values for laboratories and EC_{10}, EC_{50}, EC_{80} values at 5 min of exposition (median of six batches); (c) z-score values for laboratories and EC_{10}, EC_{50}, EC_{80} values at 15 min of exposition (median of six batches). Dotted lines show the z-score classification (satisfactory ($|z| \leq 2$), questionable ($2 < |z| \leq 3$), unsatisfactory ($|z| > 3$)).

tion before toxicity analysis can induce to a better performance of toxicity measurements. On the other hand, wastewater samples are also degradable and higher deviation than in toxicant references should be expected. Fig. 4 shows mean and median of EC_{10}, EC_{50}, EC_{80} values at 5 and 15 min. Similarly to toxicant references, mean is higher than median. S.D. and MAD for EC_{10} are higher than EC_{50} and EC_{80}. It is notable the high S.D. and MAD values for EC_{50} at 15 min. As well as EC_{80} median is more robust than EC_{10} and EC_{50} at 5 and 15 min. On the other hand, EC_{80} gives an idea of the toxicity (80% inhibition) of the wastewater, since correspond to a percentage of dilution of 25–27%. But, with this dilution, turbidity of the sample also can contribute to the toxicity of the sample.

Data set corresponding to laboratories and batches of samples at 5 and 15 min showed z-scores values ± 2 for 80% of data. Fig. 5a is an example of z-score values for laboratories and batches that correspond to EC_{50} at 15 min. Fig. 5b illustrate z-score values by laboratories and EC_{10}, EC_{50} and EC_{80} values at 5 min, where 83% of results had a z-scores values ± 2. Unsatisfactory results (z-score > 3) related to the determination of EC_{50} were observed for laboratories with codes 1, 8, 9. z-Score values <3 related to EC_{10} were observed for laboratories 8 and 11. Fig. 5c shows z-score values for laboratories and EC_{10}, EC_{50}, EC_{80} values at 15 min, where 70% of results were also satisfactory. Similar trend was observed at 5 min. Using FFP, more than 76 of the results is also considered acceptable assuming a standard uncertainty of 30%. Thus, the reproducibility and stability observed can be considered as satisfactory following z-score classification in the 80% of data sets. On the other hand, the processing of samples (centrifugation and filtration) previous to toxicity analysis can be favorable to obtain satisfactory results on the basis of the reproducibility observed.

4. Discussion

A common way to establish inter-laboratory comparisons for performance assessment is the use of measurement results of the participants to calculate the assigned value of the measurand and the associated uncertainty. There are well known and statistically sound methods available to combine results with different uncertainties [24]. Parametric statistic is the more commonly known approach. One of the characteristic of parametric statistic (e.g. mean and S.D.) is the great sensitivity for deviating results. Thus, the use of classical statistical techniques usually require the application of outliers tests (e.g. Grubb's, Dixon's or Cochrane's tests) to remove the influence of deviating results (e.g. outliers, stragglers) before that the mean and S.D. are calculated. Non-parametric statistic approach is also valid with test results that do not have a normal (Gaussian) distribution. This is advantageous in proficiency tests as anormal distributions are frequently encountered. To analyze test data reported from participant laboratories and to evaluate the analytical performance, robust statistical techniques were used in accordance with the annex A in the ISO/IEC Guide 43-1 [25]. As well as parametric statistic were also applied as approach for an initial comprehensive analysis of the inter-laboratory exercise.

In contrast to parametric statistic, outlier techniques are not required in robust statistic, because deviating test result do not have a great influence on the estimate of the location and spread of the test results. The use of robust statistic can minimize the influence that extreme results may have on estimates of the mean and standard deviation. Hence, outliers were not excluded before calculation of variability measures for the participant laboratories.

In common statistics for relative comparison of results and evaluation of performance of laboratories, the results of participants are usually converted into a z-score. Thus, for further interpretation of the data, median of results of laboratories was used as the assigned value as well as the corresponding MAD to obtain the z-score and classification was applied.

In addition, to evaluate absolute performance, criteria based on "fitness for purpose" (FFP) or expert criteria based on the analyst background can be applied. In the absence of performance characteristics that defined a level acceptable for the uncertainty, a defined value based on the FFP principle (target robust standard deviation) can be selected as criterion. In this inter-laboratory study, z-score was also calculated establishing robust S.D. to range of $\pm 30\%$. This indicates that the selected performance criterion (30% deviation from the assigned value) represents an uncertainty range that is "fit for purpose" for evaluating the measurement results and performance of the participants. This selection was derived from previous reported inter-laboratory studies and validation studies with the *V. fischeri* test [7,17,19].

5. Conclusions

Parametric and non-parametric statistics have been applied and performance of participant laboratories has been evaluated by monitoring the z-scores. Based on z-score classification, more than 70% of the laboratories showed a satisfactory performance for phenol, 3,5-dichlorophenol and influent wastewater (86%, 90% and 70%, respectively). Reproducibility and stability was observed in toxicant references and in wastewater samples. EC_{80} determination appears to be more robust that EC_{10} and EC_{50}. EC determinations can be considered favorable at 5 and 15 min of exposition, in particular for EC_{80}. The use of robust statistic is an appropriate approach because problems related to big dispersion of results (outliers) are minimized as well as its use is indicated when the number of participant laboratories is low. The use of different commercial devices can not be considered an additional source of variation.

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