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COMMITTEE OF EXPERTS ON THE TRANSPORT OF DANGEROUS GOODS AND ON THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS

Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals

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UPDATING OF THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS (GHS)

Environmental hazards

Scientific issue paper related to the development of a classification scheme to accommodate chronic toxicity to aquatic organisms for assigning a chronic hazard category

Transmitted by the Organization for Economic Co-operation and Development (OECD

Background

1. In December 2002, the UN Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) requested the OECD to start a further *"development of the classification scheme to accommodate chronic toxicity to aquatic organisms for assigning a chronic hazard category"* during the biennium 2003-2004. In addition, in December 2004, the Sub-Committee renewed the mandate and requested the *"submission of a scientific issue paper to be completed in 2005"*.

2. This paper summarizes the scientific background and the basis required for the identification of chronic hazards relevant for aquatic organisms.

Current Classification System

3. The current classification scheme for hazardous substances to the aquatic environment includes three categories for addressing the acute hazards and four categories for covering the chronic hazards. The acute aquatic hazard of a substance is assumed to be directly associated with its short-term toxicity to aquatic organisms. Therefore, the criteria for setting the acute hazard categories are based exclusively on the acute L(E)C50 data. Three main taxonomic groups, representing different trophic levels are considered, fish, crustaceans and algae/aquatic plants. Usually, the classification is based on the lowest valid toxicity value.

4. However, the criteria for setting chronic hazards are substantiated on different basis. From a scientific perspective, two complementary grounds should be identified. Categories Chronic 1 to 3 are created by the combination of acute toxicity (using the same criteria and cut-offs selected for the acute hazards) and two fate properties, lack of rapid degradation and bioaccumulation potential. The fate data qualifies the hazard identified by the acute toxicity; the chemical's lack of rapid degradation in the aquatic compartment and/or its bioaccumulation potential in aquatic organisms are used as indicators of the potential of that substance for causing long term effects. The experimental demonstration of low chronic toxicity (chronic NOEC > 1mg/L, or at the solubility level) is used as declassification criterion.

5. This system is known as the "surrogate system" for chronic classification based on acute toxicity and fate data (degradability and bioaccumulation).

6. Chronic Category 4 is substantiated under related but different grounds. This category is introduced in the current system as a "safety net" classification for use when the data available do not allow classification under the formal criteria but there are nevertheless some grounds for concern. This category covers the technical limitations of acute toxicity tests for measuring the hazard of some chemical groups such as poorly soluble chemicals that are not acutely toxic at concentrations equal to their water solubility limit. However, the precise criteria are not defined with one exception. For poorly water-soluble organic substances for which no acute toxicity has been demonstrated, classification can occur if the substance is both not rapidly degraded and has a potential to bioaccumulate. In order to prevent the classification of non-hazardous chemicals, the declassification criteria based on chronic toxicity (i.e. chronic NOECs >1 mg/l or > water solubility) is also included [See GHS Par. 4.1.2.12 (UN 2005)].

7. The scientific bases supporting this category are clear: for chemicals which are not rapidly degraded and have bioaccumulation potential, the lack of acute toxicity does not necessarily reflect an absence of hazard. Typical examples are poorly soluble chemicals where lack of acute lethality at the solubility limit may coexist with a chronic NOEC well below 1 mg/l. In such circumstances, consideration should be given to whether the Chronic 4 category should apply [See also GHS Par. A9.3.5.7.1 and A9.3.5.7.2 (b) (UN 2005)]. Other examples are chemicals with very sensitive modes of action on reproductive endpoints which do not result in lethal effects, such as endocrine disrupters.

8. The historic development, scientific basis and results of aquatic hazards identification systems have been reviewed in the GHS and also elsewhere (Lundgren, 1992; Hart et al., 1998; Wells et al., 1999. Licht et al., 2004).

Test methods and endpoints for acute and chronic toxicity

9. The starting point for accommodating chronic toxicity data into the aquatic hazards classification scheme is the selection of relevant chronic values. The GHS already includes recommendations and guidance in relation to acute and chronic toxicity data [see Chapter 4.1 *Hazards to the Aquatic Environment*, and Annex 9 *Guidance on Hazards to the Aquatic Environment*, in particular Section A9.3.3.2 (UN 2005)].

10. The use of a battery of tests for chronic effects on three different taxa and the lowest NOEC is similar to the approach of the GHS with respect to the use of acute ecotoxicity data. Similarly, one valid chronic test data can be used for classification purposes even though other chronic tests data do not warrant classification. The scientific justification for this statement is clear, as the test battery covers a set of relevant taxonomic groups essential for maintaining the structure and function of aquatic ecosystems.

11. However, from a scientific perspective and looking at the OECD and related test guidelines, a clear distinction between animals (vertebrate and invertebrates) and algal/plant tests must be considered.

12. For animals, the acute and chronic tests present clear differences in exposure times, measured endpoints and reported values.

13. Basically, the acute guidelines offer short-term (few days) lethality assays where the LC50 (or the EC50 for a closely related parameter such as immobilization for daphnids) is measured. However, the chronic toxicity guidelines offer a very different approach. The test duration is related to the life cycle of the organism and, therefore, can be very different (days, weeks, months); sublethal endpoints are measured instead of lethality; variability among the measured endpoints in the different assays is high; and the NOEC instead of the LC50 is used.

14. The use of the NOEC for presenting chronic effects has been debated for decades due to its statistical and methodological advantages and disadvantages. There are several claims for replacing the NOEC by more statistically suitable parameters such as the ECx. This discussion is outside the scope of this paper as both the NOEC and ECx are included in the GHS [Paragraphs 4.1.1.6, A9.3.2.2 and A9.3.3.2.1 (UN 2005) specifically offer the possibility for using ECx values]. The developments and concepts presented in this document can also be applied to expressions of chronic toxicity based on ECx. Additional guidance from the OECD is available (OECD, 1998; 2003).

15. Not all long-term tests are suitable for the identification of chronic hazards. Tests for chronic effects should cover at least the most critical stages in the life cycle and, preferably, the whole life cycle of the organisms, including reproduction and development. It is also crucial that the chronic tests to be used for chronic hazard classification last long enough so that steady state conditions are reached (i.e. that the concentration in the test organism virtually does not increase at the end of the testing period) [see also GHS Paragraph A9.3.3.2.1 (UN 2005)].

16. The information obtained from the analysed databases indicates that for algae and plants the EC50/NOEC ratios are lower than for fish and invertebrates. In fact algae/plants EC50s are not based on lethality but on growth rate or biomass production (Weyers and Wollmer, 2000;

Eberious et al., 2002). For the particular case of unicellular algae, which usually constitute the most common information, the tests from which EC50s and NOECs are derived are short-term chronic tests as they last only 3-4 days, but cover several generations; both the EC50 and NOEC cover several generations, similar exposure times, and in most cases both values are obtained in fact from the same test. [See also GHS Par. A9.3.2.7 and A9.3.3.2.3 (UN 2005)].

17. This distinction must be considered when looking for acute-to-chronic relationships. The larger differences are observed for animals; thus vertebrate and invertebrate data should receive a particular attention in this process.

Test methods for highly lipophilic substances and endocrine disrupters

18. Physicochemical properties, including lipophilicity, should be considered when interpreting data from chronic tests. Among other things the appropriate test duration will be dependant on such properties.

19. Endocrine disrupters, like some carcinogens, may produce long-term effects after short-term exposures. Hence, flexibility is needed on this issue. In relation to aquatic hazard classification endocrine disrupters will have to be looked at in the future when more progress has been achieved on their assessment. At the present time, it is suggested to consider all available test data case by case.

Acute/Chronic Toxicity Ratios and related information

20. The evaluation of acute-to-chronic ratios (ACRs) has been an important element in the discussions related to the accommodation of chronic toxicity data into the classification scheme, as the current classification scheme already includes criteria for setting chronic hazards based on acute toxicity and fate properties. The identification of ACRs has recently received a significant attention, considering differences associated to the mechanism of action (ECETOC, 2003) or even new statistical methods based on species sensitivity distributions (Duboudin et al., 2004).

21. Getting scientifically sound information on the distribution of ACRs among the universe of chemical substances was considered a critical aspect; and several experts have conducted specific analysis of nationally available databases.

22. Germany analyzed high quality validated data for pesticides, new chemicals and existing chemicals on fish, daphnids and algae. Sweden analyzed data on fish and crustaceans contained in the Nordic Substances Database (NSDB) for industrial chemicals and pesticides (http://www.norden.org/miljoe/sk/nsdp.asp). The United States analyzed the data from the USEPA Pesticide Ecotoxicity Database on fish early life stage and crustacean full life cycle.

23. Criteria for database analysis were discussed and agreed and the distributions of ACR were estimated based on different levels of certainty.

24. In addition, Denmark provided an analysis of the data included in the ECETOC Technical Report N° 91 and Spain analyzed the distribution of the data on fish, invertebrates and algae from four different sources (the EU database on pesticide, the ECB database on High Production Volume Chemicals, the USEPA-ECOTOX database and the ECETOC dataset).

Results of the ACR analyses

25. The results of the different databases were analyzed among the experts. The databases contained industrial chemicals and pesticides, as well as different levels of validation. Therefore, the combination of all available values in a single database would require a significant amount of work and in some cases was not possible due to confidentiality issues. It is also unclear that such laborious work will result in a significant added value. There was a good degree of coherence observed between the outcomes of the respective data analysis, such that no further aggregation of the datasets was needed. Due to the reasons presented above, the following figures reflect the situation for fish and invertebrates.

26. The ACR value was highly dependent on the chemical; the values cover a wide range distribution from 1 to > 100.000. The distribution is asymmetric, with a median << arithmetic mean. The distribution shape looks like a lognormal distribution, but the lognormal fitting has not been confirmed in all cases.

27. The most likely distribution median corresponds to a value of around 10. The median for pesticides seems to be slightly higher; the type of chronic tests usually available for these chemicals (reproductive chronic assays) could contribute, at least in part, for this difference.

28. The arithmetic mean is mostly between 100 and 200 but it is highly dependent on the high ACR values and therefore it is not recommended for expressing a centralized parametric value for the distribution.

Results of the additional analyses

29. Additional statistical calculations such as the Chemicals Toxicity Distributions (CTDs) confirmed the above results and offered supplementary information. It had been demonstrated previously that the CTDs for acute toxicity are loglinear distributions similar for fish, invertebrates and algae (Tarazona et al., 1996; 1999; Vega et al., 1999). The analysis of chronic NOECs also demonstrated lognormal distributions for the chronic CTDs, being similar for fish and invertebrates but clearly different for algae.

30. The Euclidian distance between the acute and the chronic CTDs can be considered the equivalent to the ACRs, but comparing the distribution shapes instead of individual values for each chemical. Two specific approaches were conducted, the first comparing the CTDs obtained for chemicals presenting both acute and chronic values, and the second comparing the CTDs obtained from the whole available information (for a large number of chemicals there are acute but no chronic data). The Euclidian distances for the CTDs based on the same set of chemicals were around 10 for fish and invertebrates, perfectly in line with the median ACR. The Euclidian distances for the CTDs based on all available information were around 100. This difference confirms that chronic data are mostly available for highly toxic chemicals as expected from regulatory needs and research interests.

31. In addition, Monte-Carlo analyses were conducted for comparing the observed chronic CTDs and those predicted from the combination of the acute CTDs and the ACR distribution. A clear deviation was observed suggesting a relationship between the acute toxicity of a chemical and its ACR. Additional studies were conducted on the Swedish and Spanish databases and the

results confirmed an inverse relationship between the acute toxicity and the ACR. Based on data analysis, the lowest ACRs seem to be found for the most -acute- toxic chemicals while the highest ACRs seem to be found for the chemicals with the lowest -acute- toxicity.

32. The coherence of the results indicates that the chronic CTDs offer a proper tool for identifying the percentage of chemicals with chronic NOECs between specific cut-off values, and therefore the percentage of chemicals that would be classified in the different categories as a function of the selected classification criteria.

Comparison of the surrogate system and the chronic NOECs

33. The potential of the acute LC50 for a specific chemical for predicting the expected NOEC for that particular chemical is poor. Predictions may cover two-three orders of magnitude. As a result classifications based either on LC50s or on NOECs would produce different results for most chemicals, independently of the selected ACR value. For an ACR=10, about 60% of the chemicals would be classified in different categories based on NOECs when compared to the classification based on LC50s. This percentage would increase to 70-80% for other ACR options.

34. Therefore, the information provided by the "surrogate data" and by the data on chronic toxicity is clearly different and must be analyzed.

35. It is clear that real NOECs from suitable chronic tests can form the basis for a chronic classification of the aquatic hazards, complementing the existing surrogate classification system in the GHS. The hazards to be covered by the chronic classification are related to the potential of the substance for provoking relevant sublethal effects such as reproduction impairment. The current testing conditions maintain the exposure over the whole assay and, therefore, do not establish differences between effects resulting from continuous exposures and delayed effects provoked by the exposure during critical windows or developmental periods (see Gonzalez-Doncel et al., 2003; 2005). Both effects are covered in chronic (life cycle and multigeneration) tests but not in acute lethality tests.

36. Consideration of bioaccumulation potential and persistence in conjunction with chronic aquatic toxicity modifies the level of concern. The role of lack of rapid degradation and bioaccumulation should be considered independently from each other. Some key criteria are presented below.

37. The degradability criterion considers that substances that do not rapidly degrade have a higher potential for a longer-term exposure over a wide temporal and spatial scale. Thus, for similar initial levels of exposure and similar chronic NOEC values, the environmental consequences of non rapidly degradable substances would generally be higher than for those that degrade rapidly. Nevertheless, long-term exposure can occur for rapidly degraded chemicals due to continuous emissions, and delayed, long-term sublethal effects can occur for some chemicals as a result of short-term exposures.

38. The current testing conditions for aquatic organisms require maintaining a constant exposure level (by using flow-through conditions or periodical water renewals) for chemicals showing a significant dissipation from the water column. Thus, degradability has no implications

for the concentration at which chronic effects are observed. However, a different situation should be considered regarding the bioaccumulation potential.

39. Generally, toxicity appears when the exposure threshold at the internal target organ is exceeded. For example, for narcotic chemicals, toxicity is directly related to the molar internal body concentration. The bioaccumulation potential reflects the time required for achieving this concentration and, therefore, some of the concerns related to this property are already included in the chronic toxicity value. Obviously, other potential concerns of bioaccumulative substances, such as those related to a longer persistence in the biota and food-web exposure, are not covered by the chronic toxicity and, therefore, for similar levels of waterborne exposure and similar chronic NOECs, the ecosystem consequences for potentially bioaccumulative substances may be higher than for those substances than do not accumulate in biota.

40. The classification based on "surrogate data" identifies a subgroup of acutely toxic chemicals, showing additional properties, which increase their potential for perturbing the environment. The combination of toxicity, non rapid degradability and bioaccumulation potential is considered in several hazard identification schemes (e.g. Wiandt and Poremski, 2002; ECB, 2003; Reemtsma and Klinkow, 2004) but it does not necessarily predict the potential for sublethal -reproductive and developmental- effects. In reality, the use of the combination of toxicity, non rapid degradability and/or bioaccumulation potential in hazard identification schemes covers a set of concerns for long-term effects including:

- Potential for biomagnification (due to a combination of both bioaccumulation and non rapid degradability);

- Exposure at levels provoking acute and/or chronic effects may persist for longer periods (due to non rapid degradation of the substance);

- Increased probability for having chronic effects (e.g. after episodic emissions the likelihood for exceeding the time-weighted average concentration provoking effects depends on the degradability of the substance);

- Delayed effects not being properly detected in standard toxicity tests;

- Duration of acute tests, which may be too brief for observing all relevant effects;

- Relevance of the dietary exposure route.

41. Interestingly, only a minor part of these concerns are covered by the chronic waterborne toxicity tests and the core part of the current classification system. Thus, when developing the classification criteria, it should be considered whether the classification based on "surrogate data" covers different long-term hazards from those related exclusively to chronic toxicity.

42. From a scientific perspective, it is essential to consider the testing strategy adopted in the current regulatory ecotoxicity tests. The rule for vertebrates and invertebrates is to focus on lethality endpoints in the acute tests and on reproduction endpoints (or growth) in the chronic tests. However, it is also possible to find some specific examples where the main effect after long-term exposure is lethality (showing a very low ACR as observed in the databases), and for chemicals producing chronic reproductive effects after short-term exposures. In addition, the

duration of the chronic ecotoxicity tests has been associated to the life cycle of the organisms, while the degradability of a chemical substance is measured using a similar time scale. Among the commonly available test results, the exposure period of an acute fish toxicity test (4 days) is quite similar to the exposure period of some invertebrate chronic reproduction tests (e.g. 7 days for *Ceriodaphnia dubia*). Therefore, in the communication strategy for chronic hazards, the pros and cons for establishing distinctions between hazards associated to long-term exposures and hazards related to sublethal (e.g. reproductive) effects should be considered.

Conclusions

43. The analysis of the available information suggests that classifications based on chronic data and "surrogate data" may cover different but complementary hazards.

44. Any substance showing a sufficiently high chronic toxicity -independently of its fate properties- represents a specific hazard and should be classified based on its chronic toxicity. The most likely distribution median corresponds to a value of around 10. In order to maintain the coherence of the current GHS while reflecting the use of a median ACR of 10, one option is to establish a scheme were the relationships between acute and chronic categories would follow this median ACR of 10. The number of categories is a regulatory issue and, therefore it has not been addressed in this scientific paper. However, the analysis of the databases has confirmed the convenience for setting categories as orders of magnitude and the need for a system covering the significant number of substances showing very very low chronic NOECs.

45. In addition, the combination of chronic toxicity and the intrinsic fate properties also modify the potential hazard of a chemical and, therefore, this possibility should also be considered when setting the classification criteria. As discussed above, degradability is an intrinsic substance property independent of chronic toxicity. Test guidelines require maintaining a constant exposure level; thus, for similar initial levels of exposure and similar chronic NOEC values, the environmental consequences of non rapidly degradable substances would generally be higher than for those that degrade rapidly . However, some relationships can be observed between chronic toxicity and bioaccumulation potential, as toxicity is related to the body burden.

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