



The added value of the 90-day repeated dose oral toxicity test for industrial chemicals with a low (sub)acute toxicity profile in a high quality dataset: An update



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ABSTRACT

A previous retrospective analysis of substances in the ECHA CHEM database concluded that, for industrial chemicals with a 'low (sub)acute toxicity profile', further testing in the 90-day study is unlikely to change this profile (Taylor et al., 2014). We have further tested this hypothesis by assessing the outcome of substances with testing proposals for which a prediction was made in that paper that the NOEL based on the 90-day study would be 1000 mg/kg bw/d. Indeed, for seven out of ten substances for which data was available, the profile was shown to be held. For three substances, the reduced NOEL was explained by renal effects in the rats, two of which had been seen in the 28-day study but had been dismissed by the study submitter. We conclude that the low toxicity profile will be even more protective if the NOEL is used from the 28-day study and an independent expert view is taken of the human relevance of any effects reported in the 28-day study.

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1. Introduction

A previously published retrospective analysis of substances in the ECHA CHEM database (Taylor et al., 2014) concluded that, for industrial chemicals with a 'low (sub)acute toxicity profile', further testing in the 90-day study is unlikely to change this profile. We defined substances with a low (sub)acute toxicity profile as those having:

- Experimental data equivalent to OECD 407 (28-day repeated dose oral study) with a reported NOEL of 1000 mg/kg bw/d or higher
- Experimental data that do not meet the criteria for classification for mutagenicity, skin sensitisation or acute toxicity by any route
- No additional evidence based on physical chemical properties, structure or use to suggest that the substance could be biologically active

For the original analysis, we required that the absence of toxicity for these endpoints needed to be supported by high quality

experimental data on the substance itself, up to the limit dose, where relevant.

Our original analysis identified 21 substances that met this definition out of only 182 substances with data from both 28-day and 90-day studies in the European Chemicals Agency (ECHA) ECHACHEM database (see www.echa.europa.eu). Of these, 20 (i.e. 95%) had a 90-day study that also reported a NOEL of 1000 mg/kg bw/d or higher. It was concluded therefore, that performing a 90-day study for low (sub)acute toxicity substances did not add any useful information to the overall toxicological dataset.

This analysis was in effect a retrospective validation of the 'low (sub)acute toxicity profile' hypothesis that had been originally proposed by the UK Health and Safety Executive (who had initially found the profile fitted 16 out of 18 substances registered under the Notification of New Substances (NONS) system) (see Taylor et al., 2014).

However, due to the low number of substances available upon which to test the hypothesis we felt that more validation would be helpful. To this end, in the same paper (4.10. Prediction of results from substances with 90-day studies proposed) we identified 14 substances which we considered may meet the low toxicity criteria out of 114 substances for which testing proposals for a 90-day study had been submitted to ECHA by the registrants. This would, in

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effect, be a prospective validation of the hypothesis since the outcome was not yet known. Naturally some time has had to pass to ensure that these substances now have the 90-day robust study summaries disseminated in the ECHACHEM database. In this communication, we are now, however, pleased to be able to present the results of the outcome of the proposed testing and a review of the robustness of the 'low (sub)acute toxicity profile' hypothesis.

2. Results

Of the 14 substances, 90-day studies were available for 12, two of which were performed using read-across substances. For the remaining two substances, the tonnage band at which the substance was registered had changed, meaning that a 90-day study was no longer required. Of the ten 90-day studies performed using the registered substances, all were performed at dose levels up to the limit dose of 1000 mg/kg bw/d. Details of the fourteen 'low (sub)acute toxicity profile' substances identified in the previous paper with testing proposals for a 90-day study are presented in Table 1.

We correctly predicted that five of ten substances with actual 90-day test data would not have a NOAEL less than 1000 mg/kg bw/d in the longer-term study (EC 641-136-6; EC 426-040-2; EC 203-838-7; EC 211-074-0; EC 203-326-3). This extends to seven out of 12 if the two substances with read across data are included (EC 402-140-1; EC 404-370-8). For one substance, we were over cautious and did not predict a NOAEL less than 1000 mg/kg bw/d, however one was reported (EC 271-237-7). We had considered that the marginal effect on red blood cell parameters noted at 300 mg/kg bw/d for males in the 28-day study could have resulted in similar or more severe effects in the 90-day, however no such effects were reported. For one substance (EC 204-111-7), we were wise to exercise caution in ascribing it to the low (sub)acute toxicity profile. A NOAEL of 15 mg/kg bw/d was reported for the 90-day study for males on the basis of renal effects. Although renal effects were also reported in the 28-day study in males at dose levels of 150 and 1000 mg/kg bw/d, these findings were considered not to be of relevance to the human risk assessment by the test submitter when deriving the NOAEL.

For three substances, effects were seen in the 90-day study that resulted in the data submitter suggesting a lower NOAEL than we had predicted (EC 230-991-7; EC 432-070-7; EC 480-370-1). For two of these, effects had been seen in the 28-day study that were disregarded by that study submitter when setting the NOAEL:

For EC 432-070-7, a number of deaths were reported in the 90-day study with this substance, the majority of which were attributed to dosing error. Transient signs of toxicity (hypoactivity, piloerection) were reported in females dosed at 1000 mg/kg bw/d. A NOAEL of 250 mg/kg bw/d was determined for this study based on changes in clinical chemistry and haematological parameters, pathology of the kidneys, bladder and stomach at 1000 mg/kg bw/d. The 28-day study for this substance reported signs of toxicity and some statistically significant changes in clinical chemistry and haematological parameters in rats administered 1000 mg/kg bw/d; findings were discounted in derivation of the NOAEL.

In the 90-day study of EC 230-991-7, one male administered the highest dose level of 1000 mg/kg bw/d was sacrificed *in extremis* on Day 33; the death is attributed to treatment but this pattern of mortality is not indicative of an effect of treatment. A number of effects at 300 and 1000 mg/kg bw/d were attributed to urolithiasis and obstructive nephropathy and a NOAEL of 100 mg/kg bw/d was therefore reported. In the 28-day study a NOEL of 200 mg/kg bw/d was based on isolated minor and reversible changes in clinical chemistry and urinalysis at 1000 mg/kg bw/d; findings are consistent with those seen in the 90-day study.

For EC 480-370-1, however, no effects on the kidneys (or other organ) were noted in the 28-day study, yet the 90-day study threw up some renal effects, resulting in a NOAEL of 100 mg/kg bw/d being reported for this substance.

3. Conclusion

We reviewed the 90-day study results of 14 substances potentially meeting the low toxicity profile predicted in Taylor et al. (2014). Of the 14 substances identified, ten now have 90-day studies available. Of these studies, six reported a clear NOAEL of 1000 mg/kg bw/d, thereby fitting the original hypothesis. (A further two reported read across data that also supports the original hypothesis). The four remaining substances have 90-day NOAELs reported to be < 1000 mg/kg bw/d; for three substances, the effects driving the 90-day NOAEL had also been reported at the same or similar dose levels in the 28-day study but had been discounted as not relevant for derivation of the NOAEL. For one of these (EC 204-111-7), which showed the most notable effects in the 90-day study out of these substances, we had been correct to register hesitation in predicting that this substance fitted the low toxicity profile. For the single remaining substance (EC 480-370-1), the renal effects in male rats driving the 90-day NOAEL were not apparent in the 28-day study.

Those substances for which the prediction was not strictly met were all characterised by renal effects seen in the rats, particularly males. Male rat-specific kidney effects are relatively common and are often dismissed as not being of relevance to humans. This perhaps explains why there was some inconsistency in the test submitters as to the consideration of the NOAEL. As explained in Taylor et al. (2014), there was limited analysis on our part of the significance of the biological results and we did not adjust the test submitter's decision on the NO(A)EL based on the 28-day study result.

In the interests of keeping the prediction model simple it is therefore perhaps advisable that any findings in 28-day studies (whether considered adverse or not) should be taken into account and the profile is considered met if there is a NOEL of 1000 mg/kg bw/d or greater in the 28-day study (rather than a NOAEL).

Had we applied this more cautious approach we would not have ascribed the low-toxicity profile to a further two substances out of the 14 substances. This would have reduced the dataset further and been slightly too sensitive (one of the four with some effects in the 28-day study was subsequently ascribed a NOAEL of 1000 mg/kg bw/d from the 90-day study). However, it would have made the prediction correct in five out of six cases (83%) or seven out of eight (88%) if the read across results are accepted.

A recent additional analysis of the ECHACHEM database by others has also provided support to the profile (Luechtefeld et al., 2016). Just using a data mining tool, they found that out of 121 substances fitting the low (sub) acute toxicity profile we suggested in Taylor et al. (2014), 70.2% also had NOAEL's greater than 1000 mg/kg bw/d based on the 90-day study. They did not do any expert screening of the data however and used the NOAEL in the 28-day rather than the NOEL (both now recommended following our follow up analysis). Nonetheless it is clear that their analysis supports our hypothesis. Furthermore, they found that if the assessment factor of 3 is applied to the 28-day study to derive a 90-day DNEL (Derived No Effect Level) (ECETOC, 2010) then only 8.3% of 122 substances had an actual 90-day based NOAEL below this.

We believe these further validations of the 'low (sub)acute toxicity profile' hypothesis should encourage chemical regulators to investigate the option to waive the 90-day study in certain circumstances. We propose that consideration is given to amending REACH, and similar legislation, such that, where both a 28-day and

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