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# MEP Order No.7 data revisions - what it means for companies

Yifei Ruan, senior consultant, and Eric Xiong, head of the industrial chemical sector, at CIRS offer advice on how to respond to recent changes in the data requirements under China's key chemical regulation MEP Order 7

The Guideline for new chemical substance notification is an essential supporting document for China's provisions on environmental administration of new chemical substances (MEP Order No 7). It has played an important role in guiding declarants on the notification of new chemical substances since Order No 7 came into effect on 15 October 2010.

The Ministry of Environmental Protection (MEP) first announced their revision to the data requirements in 2014. This was done with the purpose of optimising data requirements and reducing the notification burden on companies.

Following three years of public consultation, the revised data requirements entered into force on 15 October 2017. They changed the instructions for the notification of new chemical substances. The aim was for them to be at least as stringent as the data requirements of developed countries like those in the EU.

The change in data requirements is mainly reflected in adjustments to exemption conditions for physicochemical, toxicology and ecotoxicology endpoints, and minimum requirements for the latter two for standard notification under MEP Order No 7. This article provides a detailed interpretation of the amendments to the exemption conditions and the minimum data requirements.

## Data exemption conditions

The adjustments to the relevant exemption conditions for physicochemical, toxicology and ecotoxicology endpoints are explained in Tables 1-3 respectively.

**Table 1 - adjustments to physicochemical data exemption conditions since revision of data requirements**

| Endpoint | Revision of exemption conditions |
|---|---|
| Self-ignition temperature | Interpretation of 'non-flammable liquids in air' is added, for example, 'flash point of liquids is greater than 200℃'<br>Melting point <160℃ is replaced by ≤160℃ |
| Oxidising properties | Interpretation of 'substance being incapable of reacting exothermically with combustible materials' is added, such as 'judgements based on chemical structure (such as organics not containing oxygen and halogen atoms / containing oxygen and halogen atoms but not chemical bonding with nitrogen or oxygen / inorganics not containing oxygen and halogen atoms)'<br>'Condition 'as for solids, if oxidising property could be proven clearly through a preliminary test, then it is not necessary to conduct a complete testing' is deleted. |

| Table 2 - adjustments to toxicology data exemption since revision of data requirements | |
|---|---|
| **Endpoint** | **Revision of exemption conditions** |
| Acute dermal toxicity | Skin corrosion is added as one of the exemption conditions |
| Acute inhalation toxicity | Skin corrosion is added as one of the exemption conditions<br>Interpretation of 'inhalation particles' is added, such as 'particles of particle sizes <10μm' |
| Skin corrosion/irritation | Acute dermal toxicity is replaced by acute dermal toxicity category 1 |
| Eye irritation | 'Skin irritation toxicity is medium (and above) and skin corrosion' is replaced by 'skin irritation category 2 (and above) or skin corrosion' |
| 28-day repeated dose oral toxicity | 'Reliable repeated dose toxicity combined with reproductive and developmental toxicity screening tests' is added as one of the exemption conditions |
| 28-day repeated dose dermal toxicity | Skin corrosion is added as one of the exemption conditions |
| 28-day repeated dose inhalation toxicity | 'Material at 20°C, vapour pressure $<10^{-1}$Pa' is replaced by 'liquid material at 20°C, vapour pressure $<10^{-1}$Pa'<br>Interpretation of 'inhalable part' is added, such as' particles of particle size <10μm' |
| 90-day repeated dose toxicity | 'Toxic effects have been observed in 28-day repeated dose toxicity using the same tested animals and exposure routes' and 'no observed effect level (NOEL) is very low' are added to the exemption conditions<br>Carcinogenicity category 1 or 2 is added as one of the exemption conditions |
| Mutagenicity | 'Genotoxicity testing in vivo has been conducted and genotoxicity testing in vitro with the same genotoxic endpoint can be exempted' is added as one of exemption conditions |
| Reproductive/developmental toxicity | 'Reproduction and development screening data can be exempted when extended one-generation reproductive toxicity (Eogrts) data can be provided' is added as one of exemption conditions<br>Mutagenic substances category 1 or 2 is replaced by germ cell mutagenicity category 1 or 2 |
| Carcinogenicity | 'Interpretation of germ cell mutagenicity' is added, such as mutagenic category 1A or 1B<br>Reproductive toxicity is deleted<br>'Having combined testing of chronic toxicity and carcinogenicity' is added as one of the exemption conditions |
| Chronic toxicity | Interpretation of 'NOEL of repeated dose toxicity is very high' is added, for example, '90-day toxicity effect NOAEL ≥300mg/kg. However, except for the situation that toxic effects which may be caused by a particular molecular structure are not detected by 90-day repeated dose toxicity and a known substance with hazardous condition that cannot be detected by 90-day repeated dose toxicity may exist'<br>'Having sufficient toxicokinetic data to demonstrate the long-term toxicity of the substance' is added as one of the exemption conditions;<br>'Having combined testing of chronic toxicity and carcinogenicity' is added as one of the exemption conditions<br>Condition 'specific target organ systemic toxicity (repeated exposure) is not classified' is deleted |

| Table 3 - adjustments on ecotoxicology data exemption conditions according to comparison of data before and after revision | |
|---|---|
| **Endpoint** | **Revision of exemption conditions** |
| Daphnia acute toxicity | 'Longer-term toxicity data for test organisms of the same species, such as fish 14-day extended toxicity testing and fish chronic toxicity testing' is replaced by 'long-term toxicity data for test organisms of the same species and containing valid acute toxicity data, such as daphnia reproduction testing' |
| Fish acute toxicity | 'Long-term toxicity data for test organisms of the same species' is replaced by 'long-term toxicity data for test organisms of the same species and containing valid acute toxicity data' |
| Fish 14-day toxicity | The endpoint is deleted |
| Terrestrial biological toxicity | Interpretation of 'low soil adsorption' is added, such as 'logKow <1.5' |
| Respiration inhibition toxicity in activated sludge | Interpretation of 'information indicating that producing microbial toxicity is impossible, like low solubility' is replaced by 'information indicating that producing microbial toxicity is impossible, for example, no toxicity is shown in soil microbial-carbon/nitrogen conversion tests' |
| Absorption/ desorption | Interpretation of 'substances and their degradation products breaking down quickly' is added, for example 'hydrolysis half-life <12 h' |

Thus, it can be seen that the revised data requirements define the waiving conditions clearly, with thresholds specified under which studies for some endpoints can be waived. Companies can determine which studies can be waived and which shall be performed based on the intrinsic properties of the substance.

In addition, further exemption conditions have been added and unnecessary tests have been removed. This not only makes it easier to understand the exemption conditions but also to reduce the test costs. Companies are able to avoid more animal tests and save testing resources, in accordance with the revised data exemption conditions, which is more consistent with the '3Rs' principle required by the guidance.

## Minimum data requirements

The adjustments to the minimum data requirements for toxicology and ecotoxicology based on a comparison of the requirements before and after revision are shown below in Table 4

| Table 4 - adjustments on minimum data requirement of toxicology and ecotoxicology according to comparison of data before and after revision | | | |
|---|---|---|---|
| **Notification Tonnage** | **Endpoint** | **Before revision** | **After revision** |
| 1-10 tonnes/year | Acute toxicity | Acute oral, dermal and inhalation toxicity shall be submitted | Acute toxicity data with only one exposure route is required, based on notification usage. Acute oral toxicity is preferred |
| | 28-day repeated dose toxicity | Shall be submitted | Deleted |
| | Mutagenicity | Ames and in vitro chromosome aberration tests shall be submitted | Stage-wise testing method is adopted (see Table 5). AMEs is conducted in the first stage: if the result is positive and shows a risk of extensive exposure, then second level testing methods shall be followed |
| 10-100 tonnes/year | Toxicokinetics | Relevant information on absorption | Assessment of toxicokinetics based on available relevant data shall be submitted |

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|---|---|---|---|
| | | toxicokinetics shall be submitted | |
| | Mutagenicity | Rodent bone marrow cell chromosome aberrations or micronucleus test data shall be submitted. If toxicokinetic test results indicate that the notified substance is not absorbed or cannot reach the target tissue (bone marrow), then other testing data shall be submitted | Stage-wise testing method is adopted (see Table 5) |
| | 90-day repeated dose toxicity | Required when severe, irreversible damages are observed in 28-day repeated dose toxicity or when NOEL is low | Deleted |
| | Reproduction/ development screening test | Screening tests can be replaced by two generation reproductive toxicity data or prenatal developmental toxicity data if potential reproductive or developmental toxicity are known | Eogrts data also can replace screening tests |
| | 14-day fish extended toxicity test | Shall be submitted and can be replaced by fish chronic testing | Deleted |
| 100-1,0000 tonnes/year | Mutagenicity | Same as the requirements for 10-100 tonnes/year | Stage-wise testing method is adopted (see Table 5) |
| | Toxicokinetics | Complete toxicokinetic relevant information shall be submitted | Same as for 10-100 tonnes/year |
| | Reproduction/ development screening test | Teratogenicity and two-generation reproductive toxicity data shall be submitted | Pregnancy developmental toxicity data and two-generation reproductive toxicity data or Eogrts data shall be submitted |
| 1,000+ tonnes/year | Mutagenicity | Same as for 10-100 tonnes/year | Stage-wise testing method is adopted (see Table 5) |
| | Toxicokinetics | Same as for 10-100 tonnes/year | Same as for 10-100 tonnes/year |
| | Reproduction/ development screening test | Same as for 10-100 tonnes/year | Same as for 10-100 tonnes/year |
| | Carcinogenicity | Shall be submitted | Whether to submit the testing data or the evaluation report depends on the mutagenicity classification and the possibility of exposure |
| | Fish chronic toxicity test | Data for one of three tests is required: early life-stage toxicity test on | Only the results of fish larvae growth testing shall be submitted |

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|---|---|---|---|
| | | fish; short-term toxicity test on fish embryo-yolk sac absorption stage; or fish larval growth test | |
| | Linear reproduction test or earthworm reproduction | Not required | Required when terrestrial biological acute toxicity test shows hazardous classification based on relevant national and industry standards |

The testing method of mutagenicity after data revision is more specific, as shown in Table 5 below. One of the obvious changes is that stage-wise testing has been adopted. This means that the testing method used at any stage depends on the results of the corresponding method used during the previous stage, negative or positive.

Stage-wise testing can significantly help businesses save testing time and costs. It can bring data acquisition closer to the target of reducing vertebrate experiments as well.

**Table 5 - stage-wise testing method of mutagenicity under different notification level after data revision**

| Endpoint | Stage-wise testing method | | | | | |
|---|---|---|---|---|---|---|
| Mutagenicity | Notification classification | Bacterial reverse mutation (Ames) | In vitro chromosome aberration/in vitro micronucleus | In vitro gene mutation | In vivo gene mutation | In vivo chromosome aberration |
| | Level I | √ | | | | |
| | From Level II | √(-) | √(-) | √(-) | | |
| | | √(-) | √(-) | √(+) | √ | |
| | | √(-) | √(+) | √(-) | | √ |
| | | √(-) | √(+) | √(+) | √ | √ |
| | | √(+) | √(-) | | √ | |
| | | √(+) | √(+) | | One of the in vivo tests should be submitted and, when the result is negative, another with different genotoxicity endpoints should also be submitted | |

Key: (-) - negative results, (+) - positive results

First Stage | Second Stage | Third Stage



## Interpretation and advice

The Chinese authorities have reduced the minimum data requirements under MEP Order No 7. For instance, only one of three routes of exposure is required for acute toxicity under level I registration, the data requirement for 28-day and 90-day repeated dose toxicity studies are removed at levels II and III respectively, and only an assessment report based on available relevant data for toxicokinetics has to be provided under level II and level III standard notification.

The revision not only enables companies to save testing resources by reducing unnecessary vertebrate animal studies but also saves costs for them. At the same time, introducing the Eogrts shows that the MEP is providing more data choices for companies and following current mainstream test methods.

When you apply for notification, you should comprehensively consider the minimum data requirements, exemption conditions, testing periods and notification timelines to formulate the most optimal notification solution.

It is advisable to collect existing data and conduct a data gap analysis prior to developing testing proposals, then preferably to conduct physico-chemical, basic toxicology and ecotoxicology testing for the purpose of further judging which toxicology and ecotoxicology experiments could be exempted based on results of basic toxicology and ecotoxicology testing.

Additionally, companies should take care to understand the changes in the exemption conditions and minimum data requirements before and after data revision. They should apply stage-wise testing reasonably to avoid unnecessary repeated tests, reduce notification cost and ensure that the launch of their new chemical manufacturing or importing activities goes smoothly.

*The views expressed in this article are those of the expert authors and are not necessarily shared by Chemical Watch*