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Substance prioritisation for the development of EU Acute Exposure Toxicity Thresholds (AETLs)

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Abstract

The aim of the EU Acute Exposure project, ACUTEX, is to develop a methodology for establishing European Acute Exposure Threshold Levels, EU AETLs, for toxic substances in relation to harm to people by inhalation. The development of AETLs is initially in the context of the risks of major accidents from chemical sites and in particular their regulation through the EU 'Seveso II' Directive. It is intended that AETLs can be used within Member States, where appropriate, to inform decisions on land-use planning and emergency planning. AETLs will not have a regulatory status.

This paper describes: the selection of 21 preliminary substances to use as case studies in the development and testing of the AETL's methodology; and the development of a prioritisation methodology to inform initial substance selection for a possible further AETLs program. The work was based on consultation with experts drawn from EU major stakeholder groups. It included a Validation Exercise working with three Member States, which account for between approximately 40% and 50% of all EU Seveso II sites. From this Validation Exercise we infer that, if these three Member States are representative in terms of numbers of priority substances, then the number of EU higher priority substances for further AETLs development is unlikely to be much in excess of 50.

Keywords: Acute Exposure Threshold Level (AETL); Substance prioritisation; Seveso II Directive

1. Introduction

The process industry in the EU is large and innovative. For example, the chemicals sub-sector is responsible for over a third of world chemicals production. Yet, on average there are some 30 major accidents every year in the EU[1] and accidents worldwide have further demonstrated the potential for disaster. Probably the worst catastrophe in the history of the chemical industry was at Bhopal, India, in 1984. A dense cloud of toxic gas drifted from the site over the surrounding shanty town killing over 2000 people and permanently disabling a quarter of a million more [2].

In the EU, the risks of major accidents from chemical sites are regulated through the 'Seveso II' Directive for the Control of Major Accident Hazards Involving Dangerous Substances [3,4]. The Seveso II Directive applies to all sites holding quantities of dangerous substances above threshold tonnages specified for certain substances (termed 'Named Substances') and for Generic Categories of substances (such as substances classified as Toxic or Very Toxic). The aims of the Directive encompass both accident prevention and mitigation of the consequences of accidents to humans and to the environment. Here, accident mitigation refers to limiting the consequences of accidents through land-use planning and emergency planning including the provision of information to the public near sites. For sites with the potential to release toxic substances, decisions on accident prevention and mitigation are informed by estimations of dispersion distances for various foreseeable events based on the toxicology of the material involved and the extent and severity of likely harm.

The aim of the EU Acute Exposure project, ACUTEX, is to develop a methodology for establishing European Acute Exposure Threshold Levels, EU AETLs, for toxic substances for use, initially, in this context. A wider future context has

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[1] According to the information in the EU 'MARS' database which gives [1] 417 major accidents over 14 years for notifiable major accidents under the Seveso II Directive and the earlier Seveso I Directive.

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not been precluded. For example, one possible area of future interest is the transportation of dangerous goods. It is intended that the ACUTEX project will provide a broadly accepted, scientifically sound methodology for developing EU acute exposure thresholds which can be adapted, where appropriate, to the various national situations in land-use planning or emergency planning, and which will complement existing thresholds developed by Member States (or industry or other organisations). Additionally, it is intended that through collaboration between toxicologists in the EU, and promotion of sharing data and expertise, the overall cost of producing these thresholds will be reduced. AETLs will not have an EU regulatory status: whether and how AETLs might be used in individual Member States is the responsibility of policy makers at Member State level.

The AETLs for a substance will define the exposure conditions in terms of airborne concentration and exposure time that will produce a series of specified levels of harm to people. These levels of harm have not yet been finalised, but they are likely to range from transient discomfort at the lower end of the scale to severe long-lasting adverse health effects and, at the upper end of the scale, life threatening effects or death. Additionally, it is intended that the AETL methodology will complement the toxicological principles established in the US Acute Exposure Guideline Levels (AEGLs) program [5]. As part of the development and testing of the methodology, AETLs are being produced for 21 substances as case studies.

One possible outcome following the ACUTEX project is a further EU program of AETLs development. The decision on whether AETLs are most suitable to meet EU needs will be informed by the outcome of ACUTEX.

The ACUTEX project started in December 2002 and has a planned duration of 3 years. It is funded under the EU's Fifth Framework Programme of Research. The project has nine partner organisations in which government, researchers and industry are represented and is led by the French Institut National de l'Environment et de Risques. The project is being monitored by a Critical Review Panel comprised of a number of stakeholder interests including end-users and scientific organisations, industry and competent authorities, at local and national levels. The Critical Review Panel is chaired by the European Commission's Major Accident Hazards Bureau (MAHB). Full details of the rationale behind the ACUTEX project, including a discussion of the acute exposure values currently used in support of implementing the Seveso II Directive, are given in ref. [6].

2. Substance prioritisation for AETLs development

Substance prioritisation is important to various aspects of risk regulation and is widely carried out. A review of priority setting systems was included in the 1986 OECD expert groups' publication [7] as part of their remit to assist in the 'rational, pragmatic and cost-effective' selection of existing chemicals, while more recently an international workshop produced a framework within the context of chemical risk assessment and management [8].

As part of the ACUTEX project, the Health and Safety Laboratory (HSL) worked with the Health and Safety Executive (HSE) to develop:

- the prioritisation methodology which informed the selection by decision makers drawn from the ACUTEX project of 21 preliminary substances for AETL case studies; and
- a prioritisation methodology to inform the selection of further substances for AETLs development if an EU AETLs program goes ahead.

At each stage of the development of the methodologies, we sought the views of the major EU stakeholders represented on the Critical Review Panel in order to ensure that their priorities were fully addressed. The overall aim was to develop prioritisation methodologies that facilitate both the decision making process and its transparency by providing a common, agreed framework. This is within the context of the principles in the European Commission White Paper on Risk Governance [9] including the need for openness and the fair treatment of all Member States. A discussion of risk analysis within regulatory decision-making, based on a workshop held at the European Commission's Joint Research Centre, is given in ref. [10].

2.1. Factors of importance to stakeholders

The development of both substance prioritisation methodologies was underpinned by a stakeholder consultation exercise conducted at the outset to identify 'factors of importance' for prioritisation. The consultation exercise was initiated and coordinated by MAHB, acting as chair of the Critical Review Panel, to elicit the views of the major European stakeholders represented on the Critical Review Panel and of EU Competent Authorities and EU Candidate States. Stakeholder views included those of the European Chemical Industry Council (CEFIC) following a workshop they held on ACUTEX.

The exercise confirmed that the longer term issue for prioritisation is: 'What is the most effective choice of substances for AETL development to maximise a reduction in off-site risk/hazard to the public from major accidents at Seveso II sites, given that it is intended that AETLs can be used within Member States, where appropriate, to inform decisions on emergency planning or land-use planning?'. Addressing this longer term issue requires: identifying substances for which the off-site risk/hazard to the public is greatest; and taking account of EU policy issues[2] and making best use of resources available for mitigation activities. However, for selection of the 21 case studies it is paramount that the ACUTEX research needs (i.e. the development of the methodology for setting AETLs) are met.

We note that the issue for AETLs prioritisation is expressed in terms of off-site risk/hazard since across the EU Member States a range of hazard and risk based approaches are used in

[2] An example of an EU policy issue which may need to be taken into account is possible international collaboration by the EU on toxicological databases used to underpin threshold development.

the control of major accident hazards as regulated through the Seveso II Directive. For example, a description of the various approaches and criteria applied in EU Member States for land-use planning purposes is given in ref. [11].

3. Selection of the 21 case study substances

3.1. Scope of substances for the case studies

The scope of substances for selection as case studies was set by the Critical Review Panel. It was limited to those substances covered by the Seveso II Directive in terms of their toxic properties. These are the 'Named Carcinogens' in the Directive, and substances classified as Toxic or Very Toxic including any 'Named Substances' in the Directive. The Named Carcinogens are substances that may have a carcinogenic effect after a single exposure; the Directive lists 17 such substances (for some their salts are also considered to be Named Carcinogens). The EU classification of a substance as Toxic or Very Toxic is according to the Dangerous Substances Directive [12] and its subsequent amendments.

3.2. The prioritisation methodology for the case study substances and the preliminary substances selected

All EU Member State Competent Authorities and Candidate Countries were invited by MAHB to propose an initial list of ten substances of interest for AETLs development. These substances formed the basis for selection of the 21 case studies. Ten of the (then) 15 Member States replied. The degree of consensus in the replies was noteworthy. For example, approximately 30% of the substances within the scope of the case studies were proposed by more than one Competent Authority.

The prioritisation methodology is in the form of: 12 selection criteria with priorities as shown in Table 1; and a spreadsheet giving information such as toxicity and physicochemical properties relevant to these criteria for each substance. The spreadsheet and full details of the criteria are given in ref. [13]. For the case studies the criteria do not aim to select exclusively the highest risk substances in the EU because one aim is to test the AETL methodology against a range of substances with diverse toxicological properties. The nominated substances provide examples of 15 key adverse health effects, which were: upper respiratory tract irritation, central nervous system toxicity, acetyl cholinesterase activity, asthma, cyanide toxicity, central nervous system depression, cardiovascular toxicity, developmental toxicity, effects on fertility, eye irritation, ocular toxicity, lung damage, methaemoglobin formation, inhibition of mitochondrial transport, respiratory depression. In our opinion, the most significant toxicity endpoints that are likely to be encountered in substances of interest for further AETLs development are represented among these 15 key adverse health effects. A specific consideration was the need to include a Named Carcinogen from the Seveso II Directive. This was the only criterion that could not be met from the substances proposed by the Competent Authorities. In discussion with Critical Review Panel and ACUTEX experts, hydrazine was selected as it has appropriate data and is in relatively widespread use in the EU.

Table 2 gives the preliminary list of 21 case study substances: it may be reviewed according to the emerging findings

Table 1
Criteria for case study prioritisation with category and priority (P), where 1 = essential, 2 = highly desirable, 3 = desirable and 4 = optional

Category	P	Description
(A) In ACUTEX case studies scope	1	Select substances in scope
(B) Meet ACUTEX research needs		
(Bi) Meet needs of toxicologists for development of AETLs methodology	1	Select at least one 'Seveso II' Named Carcinogen
	1	Select one (but not more than one) substance with poor toxicological database and no AEGL
	1	Select at least three Substances with poor toxicological database for which an AEGL exists
	1	Select at least one substance with each of 15 key adverse health effects
	3	Avoid over-representation of upper-respiratory tract irritants
	3	Select one substance only from groups with very close structural and relationship and toxicological properties
(Bii) Allow comparison with US AEGLs	1	Select at least five substances with an AEGL.
(C) Maximise usefulness of 21 AETLs developed as case studies for use as appropriate in EU Member States		
(Ci) High risk/concern across EU	2	Give priority to substances nominated by more than one Member State
	4	Give priority to substances with greatest potential to cause adverse health effects, based on physicochemical and toxicological hazardous properties (optional criterion not needed in practice)
(Cii) Representative of Seveso II chemical plant	2	Select at least one solid, liquid and gas
	2	Select substances stored as liquids to cover a range of vapour pressure and toxicity

Table 2
The preliminary 21 AETL case study substances: may be reviewed according to emerging findings of AETLs methodology development

Acrylonitrile	Allylamine	Ammonia
Aniline	Carbon disulphide	Chlorine
Dichlorophenyl isocyanate	Ethylene oxide	Hydrazine
Hydrogen chloride	Hydrogen fluoride	Hydrogen sulphide
Methanol	Nitrogen dioxide	Oxybenzene (phenol)
Phorate	Phosgene	Phosphorous trichloride
Propionitrile	Sulphur dioxide	Toluene diisocyanate

of the AETLs methodology development. For example, four substances were included because they were proposed by 6 of the 10 Competent Authorities: hydrogen fluoride which is used as a catalyst in the production of lead-free petrol; chlorine which is produced in bulk for drinking-water treatment; hydrogen chloride which can be released following the spillage of various water-reactive substances; and hydrogen sulphide which is widely used as a reagent in chemicals production and which can also potentially be released as a reaction product. Aniline, a widely used starting material for the production of synthetic dyes, was selected as an example of one of the 15 key adverse health effects: it causes toxicity by reducing the capacity of the blood to carry oxygen due to the formation of methaemoglobin.

4. Substance prioritisation methodology for possible further AETLs development

The substance prioritisation methodology for further AETLs development is described below and full details are given in ref. [14]. In the event that a program of further AETLs development takes place, the methodology will be subject to further stakeholder consultation. This is to allow the methodology to be updated as necessary to take into account factors such as the money which will initially be made available for AETLs development (which in turn will affect the number of substances to be selected), and any changes to stakeholder priorities or data availability.

4.1. Scope of substances for further AETLs development

The Critical Review Panel is advising the EU Commission on the scope of substances for possible further AETLs development. (Our role has been to advise the Critical Review Panel on supporting scientific and technical issues.) The scope they are advising at this time is based on the Seveso II Directive, but additionally encompasses other substances identified by Competent Authorities as being of particular interest in terms of off-site risk/hazard. It includes substances covered by the Seveso II Directive in terms of their toxic properties, as described in Section 3.1, and also substances which are classified as Corrosive or Irritant. Corrosive and Irritant substances that are not also classified as Toxic or Very Toxic, although not relevant when determining the applicability of the Seveso II Directive to a chemical site, may be of interest for AETLs development if they can potentially be released in very large quantities from a site.

Additional categories of substance may also be considered to be in-scope on the basis of expert judgment. For example, this might include any nominated substances with data indicating a potential to induce cancer following a single exposure, but which are not Named Carcinogens in the Seveso II Directive.

The scope covers individual substances only. Mixtures of substances are out of scope because of the scientific limitations on the thresholds that toxicologists can currently develop. The importance of mixtures in terms of off-site risk/hazard due to the possibility of, for instance, synergistic effects, is recognised.

4.2. Main elements of the prioritisation methodology

Substances nominated by Member State Competent Authorities form the basis for selection of substances for further AETLs development. This is to ensure that Member State priorities will be directly reflected in the final EU list of substances for AETLs development. Additionally, we note that no existing databases with information from Member States hold sufficient information for prioritisation purposes.[3]

One criteria used to rank these nominated substances is their potential to cause off-site harm based on their inherent properties and potential release quantities during an accident at a site. These are hazard measures which are used rather than risk measures since there are no EU-wide measures or criteria for assessing off-site risk and, even if such measures did exist, the demands on Competent Authorities that providing the necessary information would entail would be wholly disproportionate to the task in hand.

At this time, information on potential release quantities is not readily available from Competent Authorities. Therefore, the potential release quantities considered for the hazard measures are the threshold site tonnages specified in the Seveso II Directive. Under this Directive, chemical sites are either 'top-tier' (Article 9) or 'lower-tier' (Articles 6 and 7) according to whether the amounts of Named Substances or Generic Categories of Substances in the Directive are above a higher or lower specified 'Qualifying Quantity'. Table 3 gives examples of Qualifying Quantities. Substances within the scope of the Seveso II Directive are initially assigned to a higher or lower priority list according to whether the nominating Competent Authority identifies a substance as contributing significantly to the off-site risk/hazard for top-tier sites, or as contributing to the risk/hazard from any Seveso II sites. For these two categories of substance, the potential release quantities considered

[3] The EU Seveso Plants Information Retrieval System, 'SPIRS' (see ref. [1]) holds information on numbers of sites for the Named Substances and Generic Categories of Substances as defined in the Seveso II Directive. However, because SPIRS is based on the requirements of the Seveso II Directive, the information is not broken down by substance within the Generic Categories. Similarly, tonnage details for EU high production substances are held in The International Uniform Chemical Information Database (IUCLID) described in ref. [15]. However, not all priority substances for AETLs development will be high production, for example those substances which are intermediates and reagents.

Table 3
Examples of Qualifying Quantities for Dangerous Substances specified in the Seveso II Directive

Dangerous substances	Qualifying Quantity (tonnes)	
	Lower-tier sites (Articles 6 and 7)	Top-tier sites (Article 9)
Phosgene (a Named Substance which is classified as Very Toxic)	0.3	0.75
Named Carcinogens	0.5	2
Very Toxic Generic Substances	5	20
Chlorine (a Named Substance which is classified as Toxic)	10	25
Toxic Generic Substances	50	200

in the hazard measures are the top-tier and lower-tier Qualifying Quantities, respectively. The Competent Authorities make these nominations based on existing national approaches used in the control of major accident hazards as regulated through the Seveso II Directive.

4.3. The hazard measures for ranking substances according to their potential to cause off-site harm

For substances which are Named Carcinogens, ranking according to their potential to cause off-site harm is done on the basis of expert judgment, while for Toxic, Very Toxic, Corrosive and Irritant substances it is based on substances' inherent properties and potential release tonnage using the hazard measures summarised in Table 4. The hazard measures allow fluids (liquids and gases) to be ranked relative to one another, and solids to be ranked relative to one another. Here, fluid and solid refer to a substance's physical state at 20 °C and atmospheric pressure. The relative ranking of fluids and solids is done on the basis of expert judgement.

For both fluids and solids there are two hazard measures. The first hazard measure gives a rough indication of the relative potential for off-site harm posed by substances independent of release quantity, that is to say determined solely on the basis of their inherent properties. The second hazard measure gives a rough indication of the relative potential for off-site harm taking potential release quantity into account.

The hazard measures use approximate $4hLC_{50}$ as an indication of relative toxicity. We note that the Seveso II Directive addresses potential off-site accidents in terms of both lethal and sub-lethal doses. The use of approximate $4hLC_{50}$ for prioritisation purposes is a pragmatic decision taken on the basis that it is the best benchmark available to allow comparison and ranking of a list of diverse substances, and that it is fit for purpose in this context.

For fluids the two hazard measures give the area in km^2 which would be covered by a plume for a hypothetical catastrophic release from a site together with supplementary information on the plume downwind extent. The area and downwind extent are for the plume's $4hLC_{50}$ footprint, that is to say the extent of the plume within which the concentration can exceed the $4hLC_{50}$. The first hazard measure uses a hypothetical 20 tonnes reference release quantity and is used to give a rough indication of the relative potential for harm independent of quantity, while the second hazard measure takes potential release quantity into account. We stress that these hazard measures are for ranking purposes only. Because the measures are based on the plume $4hLC_{50}$ footprint, the *absolute* values for the plume areas and extent are very large and are not intended to convey any meaning in relation to absolute hazard or risk.

For solids, the first hazard measure is to prioritise according to $1/4hLC_{50}$: that is to say the lower the $4hLC_{50}$ the greater the toxicity. This is based on the potential for solids to be dispersed off-site in fires (for example, warehouse fires). Not all of a solid will be dispersed in a fire plume, and some of what is dis-

Table 4
Summary of hazard measures

	Substance type		
	Toxic and Very Toxic substances	Irritant and Corrosive substances	Seveso II Named Carcinogens
Physical state at 20 °C and atmospheric pressure			
Fluids (vapours or liquids)	• 20 te plume area ($4hLC_{50}$ footprint) with supplementary information on • 20 te plume downwind extent • Qualifying Quantity plume area ($4hLC_{50}$ footprint) with supplementary information on • Qualifying Quantity plume downwind extent	Same with potential release tonnage in place of Qualifying Quantity	Expert judgment
Solids	• $1/4hLC_{50}$ • Qualifying Quantity/4hLC	Same with potential release tonnage in place of Qualifying Quantity	Expert judgment

persed will be carried sufficiently far away that it will not pose a risk. Therefore, toxicity is a very crude measure of hazard.[4] It is not intended to be a definitive scientific assessment. The second measure is to prioritise according to increasing: release quantity/4hLC_{50}.

We consider that a more detailed hazard measure for solids, in line with that for fluids, would not be appropriate because the potential for off-site harm has considerable dependence on factors that are unrelated to a substance's inherent hazardous properties. For example, factors influencing the potential for off-site harm of a substance from warehouse fires include [16–18]: the flammability and quantity of the substances it is stored with; the relative height at which the substance is stored (because of dispersal effects); the flammability and size of packaging; and the structure of the warehouse.

Here, the potential release quantity is taken to be either the Seveso II Qualifying Quantity (top-tier for the higher priority substances, or lower-tier for the lower priority substances) or, for Corrosives and Irritants, the actual potential release quantity according to information supplied by the nominating Competent Authority.

4.4. The prioritisation methodology

The prioritisation methodology may be broadly summarised as follows. Prioritisation of a substance is independent of the availability of toxicological data or the existence of other toxicity threshold values. We stress that expert judgment is required throughout the process.

(i) Member State Competent Authorities nominate substances, consulting stakeholders at national level as appropriate. They identify which of their nominated substances contribute significantly to the off-site risk/hazard from top-tier Seveso II sites, referred to as the 'higher priority substances', and which substances contribute to the off-site risk/hazard from any Seveso II sites, referred to as the 'lower priority substances'. For Corrosives and Irritants, they provide potential site release tonnage and, optionally, an indicative priority (higher or lower). Optionally, each Competent Authority also indicates: the number of sites for which the risk/hazard is dominated by each nominated substance; and whether there are any specific prioritisation factors at a national level which they wish to have taken into account.

(ii) Those nominated substances which are in scope are assigned to the preliminary higher priority and lower priority substance lists. For Corrosives and Irritants this is done according to their potential to cause off-site harm using the hazard measures. Within the preliminary higher and lower priority substance lists, the substances are ranked according to the number of Member State nominations, together with the substances' potential to cause off-site harm using the hazard measures. Optionally, the number of sites for which the risk is dominated by these substances may be used as a 'tie-breaker' where substances have a similar rank. Any additional national-level prioritisation factors raised by Competent Authorities are taken into account on a case-by-case basis. Ranking of the preliminary higher and lower priority substance lists is independent. Together with consideration of any EU policy issues, this gives a preliminary EU higher priority and lower priority list of substances for AETLs development for consultation purposes.

(iii) Proceeding in parallel with (ii), nominations are checked and additional supporting information is requested from Competent Authorities if necessary.

(iv) Following EU-level stakeholder consultation, and taking into account the costs and benefits of AETLs development, a first list of substances for AETLs development is decided. This first list might, for instance, comprise: the higher priority substances with greatest rank; or all the higher priority substances; or all the higher priority substances together with the lower-priority substances of greatest rank.

(v) AETLs are developed. During this time, the list of substances for AETLs development is kept under review according to changing stakeholder needs.

4.5. Discussion of the prioritisation methodology

At this time, the relative importance in the ranking process of the number of Member State nominations and the hazard measures for a substance has not been decided. This is a policy matter left for consideration by the Competent Authorities and the Critical Review Panel.

Also, as already noted, the methodology will be reviewed in the event that a further AETLs program is agreed. For example, if the money initially available for an AETLs program would only cover higher priority substances, then initial Member State nominations might be invited for these substances alone. Equally, ranking of these higher priority substances may be unnecessary if the funding would cover AETLs development for all of them. Similarly, any changes to data availability would need to be taken into account. For instance, if information on potential release tonnages were in future available (for example, expressed as typical tonnages of concern for a substance) the methodology could be modified accordingly.

4.6. The Validation Exercise

One requirement for the methodology was that it should use information that can be readily supplied by Competent Authorities. Also, an important need in the early stages of the methodology's development was to establish an indication of the number of EU priority substances and the degree of consensus on these substances between Member States, since this determined the degree of complexity needed. A Validation Exercise was therefore carried out which considered both data availability and numbers of substances.

The Validation Exercise was carried out working with representatives of the French, Italian and UK Competent Authorities. These three Member States account for between approximately

[4] We are grateful to Mr. R. Rowlands, a Major Hazards specialist inspector at HSE, for suggesting this hazard measure to us.

40% and 50% of all EU Seveso II sites for the 25 Member States.[5] The number of Seveso II sites in the three Member Sites is similar. As part of the Validation Exercise, the three Competent Authorities proposed 162 in-scope substances for AETL development including one substance which is in-scope as a Corrosive or Irritant. Of these 162 substances, 141 are further substances that are not included in the 21 preliminary case study substances: 19 are higher priority and 134 are lower priority. For the 19 higher priority substances, 37% (7) were proposed by at least 2 of the 3 Member States.

For example, the UK proposed 133 further substances for AETLs development. Together with the 21 preliminary case study substances, these comprise the 154 acutely toxic substances which the UK Competent Authority had previously 'screened' for their potential to pose off-site risks when giving land-use planning advice or assessing safety reports. The substances are given in the publicly available list at ref. [19]. This list was started in 1990 and gives the UK Competent Authority's toxicological threshold used for advising on land-use planning and in the assessment of safety reports provided by industry under the Seveso II and earlier Seveso I Directive. Of the further substances for AETLs development, 12 were identified as higher priority. This was based on quantitative studies of top-tier sites, which had previously been carried out for other purposes. These quantitative studies took into account issues such as inherent hazardous properties, potential release tonnage, and storage type. For these substances, information is available on the number of top-tier sites for which they dominate the off-site risk. The proposed substances and the criteria used to select them were the subject of a UK stakeholder consultation exercise. The UK's final priorities for AETLs development will depend on the outcome of ACUTEX; the information provided during the Validation Exercise was solely to inform the development of the prioritisation methodology.

4.6.1. Indication of number of further EU higher priority substances and implications

Based on the number of further higher priority substances proposed by France, Italy and the UK, and taking into account the degree of consensus in the replies, we infer that if these three Member States are representative in terms of numbers of priority substances, the total number of EU higher priority substances for further AETLs development is unlikely to be much in excess of 50. The implications of this were discussed at a Validation Workshop attended by representatives of the Critical Review Panel, the three Competent Authorities, and the Steering Committee for the ACUTEX project. While value for money considerations cannot be pre-judged, it was suggested that this outcome raises the possibility that all of the EU higher priority substances could be included in a first list of substances for AETLs development in any further AETLs programme.

[5] Information on numbers of sites was provided by MAHB. Data from some of the 25 Member States is currently being clarified or not yet held, and therefore the figures quoted are approximate only.

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Glossary

$4hLC_{50}$: the airborne concentration of a substance that will kill 50% of the population exposed for 4 h.
Acute exposure: short-term exposure, usually up to several hours duration.
Hazard: a situation with a potential for harm to people.
Risk: the likelihood (frequency) of a given degree of harm being suffered as a result of the realisation of specified hazards. That is to say, risk is a function of both likelihood and consequences. For example, risk may be expressed in terms of the likelihood of an accident at a site in which more than a specified number of people receive a specified dose or worse of toxic substances.