



INVENTORY MULTI-TIERED ASSESSMENT AND PRIORITISATION FRAMEWORK

Identification of Chemicals of Low Concern to Human Health

Introduction

This paper outlines the approaches and the sources used to identify the chemicals of low concern (CLC) to human health.

Background

To increase efficiency, the stakeholder advisory groups assisting the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) with the development of the Inventory Multi-tiered Assessment and Prioritisation (IMAP) Framework agreed that certain chemicals of inherently low concern to human health should be identified as a first step in the framework. However, no criteria to help identify such chemicals were proposed, other than polymers of low concern and specific chemicals already assessed by NICNAS.

During a pilot evaluation of the IMAP Framework, an approach was developed for identifying chemicals of low concern to human health. This approach was included into the IMAP Framework Tier I exclusion filters which identify chemicals that are not expected to pose a concern to human health as a first step prior to applying further risk characterisation tools at Tier I. This approach has identified chemicals which are not expected to pose a concern to human health at Tier I regardless of exposure and do not proceed to Tier II assessment.

The approach developed has been independently validated by Australian scientific experts.

Approach

The approach used by NICNAS to identify chemicals of low concern to human health was primarily based on the approach used by Health Canada used to set aside chemicals considered to be of low hazard as part of the Categorization of the Domestic Substances List (DSL). The approach followed the following steps:

- 1) identification of existing national or international lists of substances considered to be of low hazard or low priority for assessment;
- 2) analysis of these lists for their applicability for identifying chemicals of low concern to human health;
- 3) development of validation rules;
- 4) development of rules to identify additional chemicals generally considered of low concern to human health;

- 5) independent expert validation of the approaches and sources used to identify the chemicals of low concern to human health; and
- 6) application of the validated approaches to identify chemicals of low concern to human health in the Stage One chemicals.

Step 1: Identification of existing national or international lists of substances considered to be of low hazard or low priority for assessment

Schemes in which substances have been qualified to be of low hazard or low priority for assessment based on review and critical evaluation of data and expert peer review were identified as follows:

- Canada SimHaz-Low Hazard list
- Annex IV of the European Union (EU) Regulation that deals with Registration, Evaluation, Authorisation and Restriction of Chemical substances (REACH)
- Annex V of the EU REACH Regulation
- United States Environmental Protection Agency (US EPA) High Production Volume (HPV) Challenge Program
- Inert Ingredients Eligible for US Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) 25(b) pesticide products
- US Food and Drug Administration's (FDA) Generally Recognized as Safe (GRAS) list

Canada SimHaz-Low Hazard list. As part of the categorization activities undertaken by Health Canada, the hazards of the chemicals were assessed using a "simple hazard tool" (SimHaz tool) for which identification of high or low hazard compounds were sourced from various agencies based on weight of evidence for multiple endpoints. The SimHaz tool was restricted to hazard based systems which had a well-delineated basis and involved some level of expert consensus/international agreement. This tool considered the following lists to determine the low hazard chemicals:

- Pesticide Formulant 4A- List of minimal toxicological concern from Health Canada, Pest Management Regulatory Agency (PMRA). The list was based on US EPA Minimal Risk Inerts List 4A. The 4A list that it was based on has since been updated with the FIFRA list (discussed below).
- Draft list of chemicals that do not need assessment in the OECD High Production Volume (HPV) Chemicals Program. The OECD has recognised certain chemicals as low hazard based on their intrinsic properties. These chemicals have been provisionally set aside for further work. This list was not a stand-alone list but rather a compilation of existing lists from the US EPA and EU; these are considered separately below.

- Annex II to Council Regulation (EEC) 793/93 of 23 March 1993 on the evaluation and control of the risks of existing substances: List of substances exempt from the provisions of Articles 3 and 4. This regulation has since been repealed and replaced with Regulation (EC) No 1907/2006. The new regulation replaced Annex II with updated Annex IV (exemptions from the obligation to register in accordance with article 2(7)(a)). The annex IV was considered separately (see below).
- US EPA- HPV Challenge Program chemicals not considered to be candidates for testing under the HPV Challenge Program, based on preliminary US EPA review indicating that ‘testing using the Screening Information Data Set (SIDS) base set would not lead to further understanding of the chemicals’ properties. This included chemicals listed under HPV ‘indicator 1’. This list was considered separately (see below).

As can be seen from the descriptions of the data sources used in the SimHaz tool, significant overlap with the chemicals identified in the updated versions of these sources and applied separately may be expected.

Annex IV of the EU REACH Regulation¹. This contains a list of substances which are exempt from registration due to an expected low hazard profile on the basis that sufficient information is known about these substances for them to be considered to cause minimum risk because of their intrinsic properties. Substances included in Annex IV are exempted from registration (as well as downstream user requirements and evaluation) for all their possible uses irrespective of the tonnage at which they are manufactured or imported (currently or in the future). The European Commission established a set of criteria² to determine what was considered sufficient information. Originally, Annex IV essentially reproduced the list of substances exempt from the obligation to report information under the repealed Existing Substances Regulation (Regulation (EEC) No. 793/93. In 2008, this list was revised based on agreed hazard criteria covering data availability, physicochemical and toxicity criteria. The toxicity criteria used for inclusion or non-inclusion are similar or more conservative than those used in the IMAP Framework. As a result of the review³, three chemicals (vitamin A, carbon and graphite) were removed, in the former case due to potential toxicity, and in the latter cases due to the possibility that these CAS numbers may be used for nanomaterials.

Annex V of the EU REACH Regulation⁴. Annex V of Regulation (EC) No. 1907/2006 (REACH) sets out substances that are exempted from the registration, evaluation and downstream user provisions of REACH because registration is deemed inappropriate or unnecessary and their exemption does not prejudice the objectives of REACH.

¹ http://ec.europa.eu/enterprise/sectors/chemicals/documents/reach/review-annexes/index_en.htm#h2-4

² http://ec.europa.eu/enterprise/sectors/chemicals/files/reach/com_rev_anx_iv_criteria_en.pdf

³ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:268:0014:0019:EN:PDF>

⁴ http://ec.europa.eu/enterprise/sectors/chemicals/documents/reach/review-annexes/index_en.htm#h2-4

Some chemicals covered by Annex are not exempted from other obligations of REACH. Several entries on this Annex relate to chemicals occurring in nature that are not chemically modified. Some entries make reference to hazardous properties which are included or excluded. Importers and Manufacturers must hold data to demonstrate that the hazardous properties criteria are met. Whilst some entries list specific chemicals others are more generic. Entries listed in Annex V which were considered for relevant for inclusion in the IMAP Framework criteria for chemicals of low concern to human health are:

- substances which occur in nature, if they are not chemically modified: vegetable fats, vegetable oils, vegetable waxes; animal fats, animal oils, animal waxes; fatty acids from C6 to C24 and their potassium, sodium, calcium and magnesium salts; glycerol⁵;
- cement clinker, magnesia;
- glass, ceramic frits;
- compost and biogas; and
- hydrogen and oxygen.

US EPA HPV Challenge program. The US high production volume (HPV) chemicals are those which are manufactured in or imported into the USA in amounts greater than one million pounds per year. The US EPA HPV Challenge program used indicators to signify whether the chemical falls outside the scope of the HPV Challenge program. The chemicals under ‘indicator 1’ are generally considered safe - these chemicals (based on preliminary EPA review) were not considered a candidate for testing under the HPV Challenge program as testing would not further the understanding of the chemicals’ properties. These lists have been annotated periodically since they were first posted on October 9, 1998.

Inert Ingredients Eligible for FIFRA [Federal Insecticide, Fungicide, and Rodenticide Act] 25(b) pesticide products⁶. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) require that all pesticides, with very limited exceptions, must be registered with the US Environmental Protection Agency (EPA) before they can legally be sold or used in the USA. In 1996, the EPA exempted certain pesticides, considered to pose minimum risk to humans and the environment, from this requirement, provided the products satisfy certain conditions.

⁵ unless they meet the criteria for classification as dangerous according to Directive 67/548/EEC with the exception of those only classified as flammable [R10], as a skin irritant [R38] or as an eye irritant [R36] or unless they are persistent, bioaccumulative and toxic or very persistent and very bioaccumulative in accordance with the criteria set out in Annex XIII or unless they were identified in accordance with Article 59(1) at least two years previously as substances giving rise to an equivalent level of concern as set out in Article 57(f)

⁶ http://www.epa.gov/opprd001/inerts/section25b_inerts.pdf

These products were exempted based in part on their minimal risk status, and in part as an effort on the part of EPA to reduce the cost and regulatory burden on businesses so that the Agency could focus its limited resources on pesticides that pose a greater risk. This updates a previous list called “US EPA list 4A” which was under Pesticide Registration Notice 2000-6.

US FDA’s Generally Recognized as Safe (GRAS) list (Type 1)⁷. This list contains food substances that are not subject to premarket review and approval by FDA because they are generally recognised, by qualified experts, to be safe under the intended conditions of use. Their safety was established by a long history of use in food or by virtue of their nature. Each substance was evaluated and categorised according to hazard by scientific experts external to the FDA. Type 1 conclusion lists those substances where there is no information available on the substance that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or might reasonably be expected in the future.

Step 2: Analysis of lists for applicability for identifying chemicals of low concern to human health

The lists described above were analysed to determine their applicability for identifying chemicals of low concern.

The lists were allocated into the following four categories: updated list available; lists of chemicals identified as safe with no condition of use; lists of chemicals identified as low risk under conditions of use; and list of chemicals with reduced regulatory requirements based on their origin as follows:

Category	Identified Schemes/Lists	Used to identify chemicals generally considered as low concern.
Updated list available	<u>Pesticide Formulant 4A- Health Canada, PMRA</u> <u>Annex II to Council Regulation (EEC) 793/93</u> <u>OECD list</u>	No
Lists of chemicals identified as safe with no condition of use	US EPA HPV indicator 1, REACH Annex IV,	Yes
Lists of chemicals identified as low risk under conditions used	Inert Ingredients Eligible for FIFRA, US FDAGRAS,	Yes with validation (see below)
Lists of chemicals with reduced regulatory requirements based on their origin	REACH Annex V	Yes with validation (see below)

⁷ <http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/default.htm>

As the uses of chemicals to be assessed by NICNAS may be very different from those under which they have been considered low risk in other jurisdictions, it was considered important to apply additional validation rules on chemicals identified by the FIFRA and US FDA GRAS list to ensure that chemicals that may require assessment are not included in the chemicals of low concern to human health category. In addition, as importers and manufacturers must hold data on hazardous properties to demonstrate that criteria for exemption under REACH Annex V is met, it was considered prudent to also validate chemicals identified by this source.

Step 3: Development of validation rules

A set of validation rules was developed, wherein chemicals meeting the following criteria will be removed from consideration as being minimally hazardous:

- 1) chemicals identified as a concern or for which regulatory action has been taken overseas (Stage one rationale);
- 2) chemicals detected in international studies analysing chemicals present in the blood in babies' umbilical cords (Stage one rationale);
- 3) chemicals meeting the hazard criteria agreed by the Human Health Expert Working Group (HHEWG) for use in the IMAP Framework based on any of the following sources:
 - Hazardous Substances Information System (HSIS);
 - European Union (EU) Regulation on Classification, Labelling and Packaging (EU CLP; conversion of old EU classifications to adopted GHS);
 - International Agency for Research on Cancer (IARC);
 - National Toxicology Program - Report on Carcinogens (NTP ROC);
 - US EPA Cancer Guidelines;
 - American Conference of Industrial Hygienists (ACGIH) Categories;
 - EU list of endocrine disrupters; and
 - List of neurotoxic chemicals from ATSDR;
- 4) chemicals included in the Schedule for Uniform Scheduling of Medicines and Poisons (except where the listing is in Appendix B);
- 5) chemicals removed from Annex IV of REACH as part of the review process; and
- 6) strong or moderate acids and bases, quaternary ammonium salts, and anhydrous deliquescent materials.

Step 4: Development of rules to identify additional chemicals generally considered as low concern to human health (expert judgement)

An analysis of the chemicals internationally recognised as safe and/or of low risk has allowed NICNAS to develop criteria for identifying additional chemicals that may be considered as low concern to human health.

In the IMAP Framework, the hazard profiles of binary inorganics and organic acid salts are characterised taking into consideration the toxicity of the anion and cation respectively.

The following anions, cations and organic acids have been identified for potential inclusion in the list of chemicals generally considered safe: Na^+ , K^+ , Mg^+ , Ca^{2+} , Cl^- , CO_3^{2-} , PO_4^{3-} , NO_3^{-1} , OH^- , O^{-2} , and SO_4^{2-} and simple salts of acetate, citrates, lactates, tartrates, malates and di- and tri- phosphates. This is based on the occurrence of a number of such simple salts on the lists discussed above, and the absence of classifications under HSIS for simple salts except where these are classified for local irritant properties relating to acidity, basicity or dessication.

Whilst additional cations (ammonium, zinc and iron (including ferrous and ferric)), could be suitable there is greater uncertainty as to whether they would not require further assessment at Tier I and potentially Tier II of the IMAP Framework.

The set of validation rules developed for the lists described above are applied to any chemicals identified using these expert judgement rules, for example, NaOH would not be identified as low concern to human health on the basis of it meeting the hazard criteria agreed by the HHEWG.

As hydrates of a substance or hydrated ions are formed by association of a substance with water, the hydrates of chemicals considered as low concern to human health will also be considered as low concern to human health, as will hydrates where the anhydrous form is ruled out due to dessication effects.

Step 5: Independent expert validation of the approaches and sources used to identify the chemicals of low concern to human health

Independent expert advice was sought on the appropriateness of:

- the approaches and sources used to identify the chemicals of low concern; and
- the chemicals identified as low concern to human health in the Stage One List (see Table 2 below).

The approaches, sources and chemicals identified as low concern to human health in the Stage One List were supported with no amendment to the list required.

Step 6: Application of the validated approaches to identify chemicals of low concern to human health in the Stage One chemicals

The above lists and rules were applied to the Stage One list of 3,000 chemicals.

One hundred and thirty three (133) chemicals were common to NICNAS's Stage One list and the lists used to identify chemicals of low concern to human health (see Table 1 below). Following the application of validation rules, comparison of the lists with the Stage One chemicals identified 86 chemicals of low concern (CLC) to human health (Table 2).

While a number of chemicals in Table 2 did not meet the criteria for removal from consideration as low concern to human health, NICNAS still had some concerns about their health effects. These include several acids and acid salts which may have irritant effects and others for which a preliminary data search provides some uncertainty in concluding that they have no potential to cause adverse health effects. However the independent expert advice sought by NICNAS confirmed the suitability of considering these chemicals as of low concern to human health.

No additional chemicals of low concern to human health were identified in the Stage One list using the expert judgement rules (step 4). These criteria could be applied to help identify chemicals of low concern on the rest of the AICS.

Table 1: Breakdown of the overlap between the Stage One chemicals and lists used to identify chemicals of low concern to human health

Lists Considered	Number of Stage One chemicals	No of unique chemicals
REACH Regulation Annex IV	8	2
REACH Regulation Annex V	15	11
US HPV Indicator 1	5	1
Inert Ingredients Eligible for FIFRA 25(b) Pesticide Products	75	50
Generally Regarded as Safe (GRAS)	64	42

Table 2: Stage One Chemicals identified as low concern to human health

CAS Registry Number	AICS Chemical Name	Annex IV	Annex V	HPV Indicator 1	FIFRA	GRAS
50-70-4	D-Glucitol	x		x	x	x
50-81-7	L-Ascorbic acid	x			x	x
50-99-7	D-Glucose	x		x		
56-81-5	1,2,3-Propanetriol				x	x
57-11-4	Octadecanoic acid		x		x	
57-13-6	Urea				x	x
68-04-2	1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt				x	
77-90-7	1,2,3-Propanetricarboxylic acid, 2-(acetyloxy)-, tributyl ester				x	

Table 2: Stage One Chemicals identified as low concern to human health (continued)

CAS Registry Number	AICS Chemical Name	Annex IV	Annex V	HPV Indicator 1	FIFRA	GRAS
143-07-7	Dodecanoic acid				x	
144-55-8	Carbonic acid, monosodium salt				x	x
471-34-1	Carbonic acid, calcium salt (1:1)				x	x
527-07-1	D-Gluconic acid, monosodium salt	x				
557-04-0	Octadecanoic acid, magnesium salt				x	
557-05-1	Octadecanoic acid, zinc salt				x	
1066-33-7	Carbonic acid, monoammonium salt					x
1302-78-9	Bentonite				x	x
1309-48-4	Magnesium oxide (MgO)		x		x	x
1314-13-2	Zinc oxide (ZnO)				x	
1317-61-9	Iron oxide (Fe ₃ O ₄)				x	
1317-65-3	Limestone				x	
1327-36-2	Aluminatesilicate				x	
1332-37-2	Iron oxide					x
1332-58-7	Kaolin				x	x
1344-00-9	Aluminosilicic acid, sodium salt				x	
1344-95-2	Silicic acid, calcium salt				x	x
1592-23-0	Octadecanoic acid, calcium salt				x	x
6132-04-3	1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt, dihydrate				x	
7320-34-5	Diphosphoric acid, tetrapotassium salt					x
7447-40-7	Potassium chloride (KCl)				x	x
7487-88-9	Sulfuric acid, magnesium salt (1:1)				x	
7647-14-5	Sodium chloride (NaCl)				x	
7757-82-6	Sulfuric acid, disodium salt				x	
7757-93-9	Phosphoric acid, calcium salt (1:1)					x
7758-29-4	Triphosphoric acid, pentasodium salt					x
7778-18-9	Sulfuric acid, calcium salt (1:1)				x	
7778-80-5	Sulfuric acid, dipotassium salt				x	
7783-28-0	Phosphoric acid, diammonium salt					x
8001-26-1	Linseed oil		x	x	x	
8001-23-8	Safflower oil		x			
8001-78-3	Castor oil, hydrogenated			x		
8001-79-4	Castor oil		x	x	x	
8002-74-2	Paraffin waxes and hydrocarbon waxes				x	
8042-47-5	White mineral oil, petroleum				x	
9000-71-9	Caseins				x	x
9004-32-4	Cellulose, carboxymethyl ether, sodium salt				x	
9004-34-6	Cellulose				x	
9004-53-9	Dextrin	x			x	x
9004-62-0	Cellulose, 2-hydroxyethyl ether				x	
9005-25-8	Starch	x				x
9005-38-3	Alginic acid, sodium salt				x	
9006-04-6	Natural rubber				x	
10034-99-8	Sulfuric acid, magnesium salt, heptahydrate				x	x
10035-04-8	Calcium chloride, dihydrate					x
10101-41-4	Sulfuric acid, calcium salt, dihydrate				x	
12168-85-3	Calcium oxide silicate (Ca ₃ O(SiO ₄))				x	x

Table 2: Stage One Chemicals identified as low concern to human health (continued)

CAS Registry Number	AICS Chemical Name	Annex IV	Annex V	HPV Indicator 1	FIFRA	GRAS
14168-73-1	Sulfuric acid, magnesium salt (1:1), monohydrate					x
16389-88-1	Dolomite (CaMg(CO ₃) ₂)				x	
25496-72-4	9-Octadecenoic acid, monoester with 1,2,3-propanetriol, (Z)-				x	
31566-31-1	Octadecanoic acid, monoester with 1,2,3-propanetriol				x	
57455-37-5	C.I. Pigment Blue 29				x	
61790-53-2	Diatomaceous silica, calcined				x	x
63231-67-4	Silica gel				x	
65996-61-4	Pulp, cellulose	x			x	
65997-15-1	Cement, portland, chemicals		x			
65997-16-2	Cement, alumina, chemicals		x			
65997-18-4	Frits, chemicals		x			
68424-61-3	Glycerides, C16-18 and C18-unsaturated, mono- and di-	x				
68648-24-8	Fatty acids, vegetable oil, unsaturated		x			
68476-25-5	Feldspar, group minerals				x	
68956-68-3	Oils, vegetable		x			
68989-22-0	Zeolites, NaA				x	
93763-70-3	Perlite, expanded				x	x
112926-00-8	Silica gel, precipitated, crystalline free				x	
112945-52-5	Silica, amorphous, fumed, crystalline free				x	
1309-37-1	Iron oxide (Fe ₂ O ₃) ¹				x	x
7440-50-8	Copper ²					x
7558-80-7	Phosphoric acid, monosodium salt ³					x
7681-11-0	Potassium iodide (KI) ⁴					x
7722-76-1	Phosphoric acid, monoammonium salt ⁵					x
7758-16-9	Diphosphoric acid, disodium salt ³					x
9002-88-4	Ethene, homopolymer ⁵				x	
61789-44-4	Fatty acids, castor oil ³		x			
67701-01-3	Fatty acids, C12-18 ³		x			
67701-03-5	Fatty acids, C16-18 ³		x			
67701-08-0	Fatty acids, C16-18 and C18-unsaturated ³		x			
67701-11-5	Fatty acids, C14-18 and C16-18-unsaturated, sodium salts ³		x			

¹ Although classified as IARC Category 3 and hence meeting the criteria for removal, the review of the IARC documentation leads to minimal concern as evidence in animals suggests a *lack of carcinogenicity* (<http://www.inchem.org/documents/iarc/suppl7/haematite.html>).

² Preliminary data search provides some uncertainty about the potential for adverse health effects however chemical is an essential trace nutrient to all higher plant and animal life and has a long history of use in food contact materials.

³ Uncertainty over potential for eye irritation effects.

⁴ Preliminary data search provides some uncertainty about the potential for adverse health effects however chemical is used as food additive i.e. iodized salt.

⁵ Although classified as IARC Category 3 and hence meeting the criteria for removal this categorisation related to subcutaneous implants which is not considered relevant to industrial uses and therefore this chemical has been included (<http://www.inchem.org/documents/iarc/vol19/ethyleneandpolyethylene.html>).