# Supplementary information – Search strategy

Table S1 – List 1 of search terms or expressions relating to mixture toxicology and number of hits in three literature databases (March 2018). Terms yielding less than 300 hits are highlighted in orange and were added (using Boolean operator ‘OR’) rather than combined (using Boolean operator ‘AND’) with terms from list 2 in the search strategy.

|  |  |  |  |
| --- | --- | --- | --- |
| **Search term** | **Web of Science** | **PubMed** | **Scopus** |
| "combin\* effect" | 15700 | 6107 | 378995 |
| “binary mixture” | 5078 | 2164 | 9656 |
| “complex mixture” | 3346 | 1316 | 18941 |
| "combin\* action" | 3036 | 1207 | 4737 |
| “joint action” | 2070 | 1036 | 4780 |
| “joint effect” | 2048 | 806 | 2770 |
| “mixture toxicity” | 681 | 443 | 659 |
| "combin\* response" | 320 | 161 | 263 |
| “chemical mixture” | 237 | 160 | 545 |
| “joint toxicity” | 214 | 132 | 916 |
| “joint response” | 160 | 77 | 536 |
| “binary combination” | 152 | 72 | 360 |
| “toxic\* interaction” | 148 | 50 | 259 |
| “multi-component mixture” | 126 | 22 | 478 |
| “mixture interaction” | 36 | 17 | 133 |
| “chemical cocktail” | 28 | 15 | 52 |
| “multi-agent mixture” | 1 | 0 | 2 |

Table S2 – List 2 of search terms or expressions relating to mixture effects and number of hits in three literature databases (March 2018). Terms yielding less than 300 hits are highlighted in orange and were added (using Boolean operator ‘OR’) rather than combined (using Boolean operator ‘AND’) with terms from list 1 in the search strategy.

|  |  |  |  |
| --- | --- | --- | --- |
| **Search term** | **Web of Science** | **PubMed** | **Scopus** |
| antagonis\* | 161383 | 356353 | 331820 |
| synerg\* | 131026 | 85964 | 156561 |
| potentiation | 26013 | 13675 | 62507 |
| “response surface” | 28555 | 6558 | 34115 |
| “response inhibition” | 5369 | 2570 | 3068 |
| non-additi\* OR nonadditi\* | 4063 | 1609 | 4628 |
| non-interacti\* OR noninteracti\* | 6402 | 1545 | 7299 |
| “hazard ind\*” | 1635 | [660](file:///C:\Users\Olwenn\Dropbox\JRC\Protocol%20development\Protocol%20sections\Search%20strategy\pilot%20searches\Search%20strategy.xlsx#RANGE!_ftn2) | 2267 |
| Loewe | 116 | 608 | 164 |
| “relative potency” | 627 | 562 | 881 |
| “toxic equivalen\*” | 1585 | [450](file:///C:\Users\Olwenn\Dropbox\JRC\Protocol%20development\Protocol%20sections\Search%20strategy\pilot%20searches\Search%20strategy.xlsx#RANGE!_ftn1) | 1368 |
| “independent action” | 605 | 447 | 962 |
| “concentration additi\*” | 993 | [412](file:///C:\Users\Olwenn\Dropbox\JRC\Protocol%20development\Protocol%20sections\Search%20strategy\pilot%20searches\Search%20strategy.xlsx#RANGE!_ftn5) | 1542 |
| “negative interaction” | 775 | 407 | 1918 |
| isobologram | 377 | 352 | 475 |
| “component-based” | 5089 | 341 | 11664 |
| “response modulation” | 385 | 265 | 408 |
| supra-additiv\* | 237 | 244 | 254 |
| “Hill equation” | 362 | 225 | 702 |
| “\*similar\* acti\*” | 444 | [177](file:///C:\Users\Olwenn\Dropbox\JRC\Protocol%20development\Protocol%20sections\Search%20strategy\pilot%20searches\Search%20strategy.xlsx#RANGE!_ftn6) | 4126 |
| “dose additi\*” | 295 | [149](file:///C:\Users\Olwenn\Dropbox\JRC\Protocol%20development\Protocol%20sections\Search%20strategy\pilot%20searches\Search%20strategy.xlsx#RANGE!_ftn4) | 403 |
| “toxic unit” | 171 | 145 | 352 |
| subadditiv\* | 886 | 134 | 935 |
| Chou-Talalay | 142 | 130 | 144 |
| superadditiv\* | 463 | 120 | 485 |
| “Bliss independence” | 80 | 79 | 89 |
| “effect inhibition” | 182 | 77 | 389 |
| “potency ratio” | 64 | 73 | 107 |
| “independence model” | 166 | 57 | 281 |
| “response additi\*” | 551 | [53](file:///C:\Users\Olwenn\Dropbox\JRC\Protocol%20development\Protocol%20sections\Search%20strategy\pilot%20searches\Search%20strategy.xlsx#RANGE!_ftn8) | 962 |
| “effect modulation” | 90 | 35 | 146 |
| “additive dose” | 107 | 32 | 145 |
| “dose summation” | 32 | 31 | 47 |
| infra-additiv\* | 27 | 29 | 30 |
| “effect enhancement” | 109 | 23 | 175 |
| “toxic\* enhancement” | 31 | [18](file:///C:\Users\Olwenn\Dropbox\JRC\Protocol%20development\Protocol%20sections\Search%20strategy\pilot%20searches\Search%20strategy.xlsx#RANGE!_ftn9) | 41 |
| “effect additi\*” | 692 | [12](file:///C:\Users\Olwenn\Dropbox\JRC\Protocol%20development\Protocol%20sections\Search%20strategy\pilot%20searches\Search%20strategy.xlsx#RANGE!_ftn7) | 1762 |
| median-effects | 344 | 11 | 391 |
| “fixed-ratio design” | 7 | 9 | 11 |
| “response augmentation” | 13 | 8 | 22 |
| “effect summation” | 11 | 7 | 15 |
| “response summation” | 8 | 4 | 10 |
| “additivity ind\*” | 25 | [3](file:///C:\Users\Olwenn\Dropbox\JRC\Protocol%20development\Protocol%20sections\Search%20strategy\pilot%20searches\Search%20strategy.xlsx#RANGE!_ftn3) | 24 |
| MixLow | 3 | 3 | 4 |
| coalism | 1 | 2 | 2 |
| “effect augmentation” | 4 | 1 | 10 |
| “integrated additivity” | 1 | 0 | 1 |
| inertism | 0 | 0 | 0 |

Table S3 – Search strategy. The only built-in filter available in PubMed is ‘Species’ and this was not considered appropriate and therefore not used in the final search strategy. When available, ‘subject area’ filters were used.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Web of Science** | **PubMed** | **Scopus** |
| MixTox - Search 1 | Search [<300 hits, OR] | 1079 | 698 | 707 |
| MixTox - Search 2 | Search [>300 hits, OR] | 31949 | 12897 | 80518 |
| Characterisation - Search 3 | Search [<300 hits, OR] | 1843 | 2088 | 1646 |
| Characterisation - Search 4 | Search [>300 hits, OR] | 367231 | 451916 | 575905 |
| 5 | 1 OR 3 | 2877 | 2753 | 2346 |
| 6 | 2 AND 4 | 2777 | 1983 | 6877 |
| 7 | (1 OR 3) OR (2 AND 4) | 5484 | 4590 | 8983 |
| Filtered by relevant subject areas | #7 | 3,048[[1]](#footnote-1) |  | 3,848[[2]](#footnote-2) |
| Filtered by species (NOT Human) |  |  | 1,748 |  |

1. **Web of Science ‘Subject Area’ filter:**

   Refined by: [excluding]: RESEARCH AREAS: (ENGINEERING OR ONCOLOGY OR MATERIALS SCIENCE OR PHYSICS OR COMPUTER SCIENCE OR MATHEMATICS OR ENERGY FUELS OR RADIOLOGY NUCLEAR MEDICINE MEDICAL IMAGING OR POLYMER SCIENCE OR ENTOMOLOGY OR NUCLEAR SCIENCE TECHNOLOGY OR GENETICS HEREDITY OR OPTICS OR PSYCHIATRY OR GENERAL INTERNAL MEDICINE OR GEOLOGY OR BEHAVIORAL SCIENCES OR BIOPHYSICS OR ANESTHESIOLOGY OR CONSTRUCTION BUILDING TECHNOLOGY OR INTEGRATIVE COMPLEMENTARY MEDICINE OR THERMODYNAMICS OR SPECTROSCOPY OR METALLURGY METALLURGICAL ENGINEERING OR MECHANICS OR BUSINESS ECONOMICS OR ELECTROCHEMISTRY OR INSTRUMENTS INSTRUMENTATION OR HISTORY PHILOSOPHY OF SCIENCE OR METEOROLOGY ATMOSPHERIC SCIENCES OR SURGERY OR MATHEMATICAL METHODS IN SOCIAL SCIENCES OR ASTRONOMY ASTROPHYSICS OR SPORT SCIENCES OR ACOUSTICS OR TELECOMMUNICATIONS OR AUTOMATION CONTROL SYSTEMS OR DENTISTRY ORAL SURGERY MEDICINE OR EDUCATION EDUCATIONAL RESEARCH OR PHYSICAL GEOGRAPHY OR LEGAL MEDICINE OR MUSIC OR OPERATIONS RESEARCH MANAGEMENT SCIENCE OR MEDICAL LABORATORY TECHNOLOGY OR MEDICAL INFORMATICS OR SOCIAL SCIENCES OTHER TOPICS OR ARCHAEOLOGY OR HEALTH CARE SCIENCES SERVICES OR IMAGING SCIENCE PHOTOGRAPHIC TECHNOLOGY OR CRYSTALLOGRAPHY) [↑](#footnote-ref-1)
2. **Scopus search query**:

   ( ( TITLE-ABS-KEY ( "combin\* effect" OR "binary mixture" OR "complex mixture" OR "joint effect" OR "combin\* action" OR "joint action" OR "chemical mixture" OR "mixture toxicity" OR "combin\* response" OR "binary combination" OR "multi-component mixture" OR "toxic\* interaction" ) AND PUBYEAR > 2006 ) AND ( TITLE-ABS-KEY ( antagonis\* OR synerg\* OR potentiation OR "response surface" OR "component-based" OR non-interacti\* OR noninteracti\* OR non-additi\* OR nonadditi\* OR "\*similar\* acti\*" OR "response inhibition" OR "hazard ind\*" OR "negative interaction" OR "effect additi\*" OR "concentration additi\*" OR "toxic equivalen\*" OR "independent action" OR "response additi\*" OR subadditiv\* OR "relative potency" OR "Hill equation" OR superadditiv\* OR isobologram OR "response modulation" OR "dose additi\*" OR median-effects OR "effect inhibition" OR "toxic unit" ) AND PUBYEAR > 2006 ) ) OR ( ( TITLE-ABS-KEY ( "joint toxicity" OR "joint response" OR "mixture interaction" OR "chemical cocktail" OR "multi-agent mixture" ) AND PUBYEAR > 2006 ) OR ( TITLE-ABS-KEY ( "independence model" OR supra-additiv\* OR "effect enhancement" OR loewe OR "effect modulation" OR "additive dose" OR chou-talalay OR "potency ratio" OR "Bliss independence" OR "dose summation" OR "toxic\* enhancement" OR infra-additiv\* OR "additivity ind\*" OR "response augmentation" OR "effect summation" OR "fixed-ratio design" OR "response summation" OR "effect augmentation" OR mixlow OR coalism OR "integrated additivity" ) AND PUBYEAR > 2006 ) ) AND ( EXCLUDE ( SUBJAREA , "MEDI" ) OR EXCLUDE ( SUBJAREA , "ENGI" ) OR EXCLUDE ( SUBJAREA , "CENG" ) OR EXCLUDE ( SUBJAREA , "MATE" ) OR EXCLUDE ( SUBJAREA , "PHYS" ) OR EXCLUDE ( SUBJAREA , "MATH" ) OR EXCLUDE ( SUBJAREA , "COMP" ) OR EXCLUDE ( SUBJAREA , "ENER" ) OR EXCLUDE ( SUBJAREA , "SOCI" ) OR EXCLUDE ( SUBJAREA , "PSYC" ) OR EXCLUDE ( SUBJAREA , "NURS" ) OR EXCLUDE ( SUBJAREA , "ARTS" ) OR EXCLUDE ( SUBJAREA , "DECI" ) OR EXCLUDE ( SUBJAREA , "BUSI" ) OR EXCLUDE ( SUBJAREA , "HEAL" ) OR EXCLUDE ( SUBJAREA , "DENT" ) OR EXCLUDE ( SUBJAREA , "ECON" ) ) [↑](#footnote-ref-2)