



Toxic Load Indicator

A new tool for analyzing and evaluating pesticide use

Introduction to the methodology and its potential for evaluating pesticide use

Lars Neumeister

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Acronyms

AbTF	Aid by Trade Foundation
ADI	Acceptable Daily Intake
a.i.	(pesticide) active ingredient
AOEL	Acceptable Operator Exposure Level
BCF	Bioconcentration Factor
BCI	Better Cotton Initiative
CmiA	Cotton made in Africa
CMR	Carcinogenicity, Mutagenicity, Reproductive and developmental toxicity
COMPACI	Competitive African Cotton Initiative
EC50	Effective Concentration, 50%
EIQ	Environmental Impact Quotient
ETL	Environmental Toxic Load
EU	European Union
FAO	United Nations Food and Agriculture Organization
GHS	Globally Harmonized System
GUS	Groundwater Ubiquity Score
HHPs	Highly Hazardous Pesticides
IARC	International Agency for Research on Cancer
ICAC	International Cotton Advisory Committee
JMPM	The FAO/WHO Joint Meeting on Pesticide Management
LC50	Lethal Concentration, 50%
LD50	Lethal Dose, 50%
LR50	Lethal Rate, 50%
MSI	Materials Sustainability Index (forms part of the Higg Index)
NOAEL	No Observed Adverse Effect Levels
OSPAR	Oslo and Paris Conventions for the protection of the marine environment of the North-East Atlantic
SEEP	ICAC Expert Panel on Social, Environmental and Economic Performance
TLI	Toxic Load Indicator
US-EPA	United States Environmental Protection Agency
WHO	United Nations World Health Organization

Introduction

Cotton cultivation is under global surveillance, and pesticide use is one hot spot issue concerning sustainability in cotton production. In the early 1990s, the organic movement was the first approach to change cotton cultivation for the better, and in the early 2000s, several other organizations took a stand to improve the economic, ecological and social performance in cotton production. Different approaches, the Aid by Trade Foundation with its Cotton made in Africa Standard, the Better Cotton Initiative and the Fairtrade Standard for cotton, to name the most recognized amongst them, were developed. With respect to pesticides, a number of specific, hazardous substances are prohibited under these standards¹.

Since then, monitoring and evaluation with a clear focus on impact assessment are on the agenda of the international textile industry, retailers, NGOs and other interest groups. Comparing the impact of materials used in the textile industry has become as important as comparing impacts of cotton produced under different cultivation systems.

Several approaches exist, trying to assess the impacts pesticides cause in the cultivation of cotton or other crops. The measurement of the total volume of pesticides applied, such as the Better Cotton Initiative (BCI) has done in previous harvest reports², is a first step, but this approach has a number of shortcomings.

The amount of applied pesticides does not give a direct indication on the possible impacts these chemicals might have on humans or the environment. A reduction of volume does not necessarily lead to a (similar degree of) risk reduction.

Against this background, the Aid by Trade Foundation (AbTF) took a proactive step and asked for advice on how to monitor the impacts pesticides may have for people and the planet beyond a “*pounds on the ground*” approach. Different existing methodologies used as pesticides impact indicators were assessed³, and the methodology of a comprehensive Toxic Load Indicator (TLI) proposed.

In order to increase the attention of and assess the perception of the TLI methodology, as well as evaluate its wider utilization potential, AbTF introduced the methodology to the Better Cotton Initiative. Jointly, the two Sustainable Standard Initiatives decided to gather feedback from experts, and therefore invited in 2015 to an Expert Panel Meeting and asked for more feedback from a number of additional experts – who could not attend the meeting itself⁴.

¹ Additionally, different methodologies of an Integrated Plant and Pest Management became mandatory. This publication focuses on pesticides, and therefore does not go into details how pesticide use shall be reduced to a last resort in pest management.

² e.g. BCI (2015): Better Cotton Initiative 2014 Harvest Report, available at <http://bettercotton.org/wp-content/uploads/2013/12/FINAL-HARVEST-REPORT-2014-updated-2pg1.pdf>

³ The review done end of 2013 included ICAC’s Guidance Framework on Sustainability in Cotton, Alterra’s Environmental Toxic Load Indicator (ETL), the Environmental Impact Quotient (EIQ) by Kovach et al from Cornell University and SAC’s Higg Index with Nike’s MSI/Green Chemistry approach. References to the primary sources can be found in chapter 6 Literature.

⁴ For more details, see the acknowledgements section of this document.

In this document, chapters 1 to 3 describe the methodology for the Toxic Load Indicator, chapter 4 reflects on data availability for the different parameters, the need for updating the scores and highlights essential requirements on pesticide use reporting in order to ensure a meaningful application of the TLI to pesticide use. Finally, chapter 5 deals with the advantages and limitations of the methodology, which is clearly hazard-based, and cannot serve as a risk assessment tool.

1. Development of a comprehensive Toxic Load Indicator

1.1 Evaluation of Toxicity of Pesticides

Measuring toxicity always needs a reference parameter. Data on toxicity is mostly generated through laboratory tests (long-term/ short-term) and/ or epidemiological studies. Due to exposure to multiple agents and factors, data from recent epidemiological studies are usually not sufficiently accurate to make an assessment for an individual pesticide.

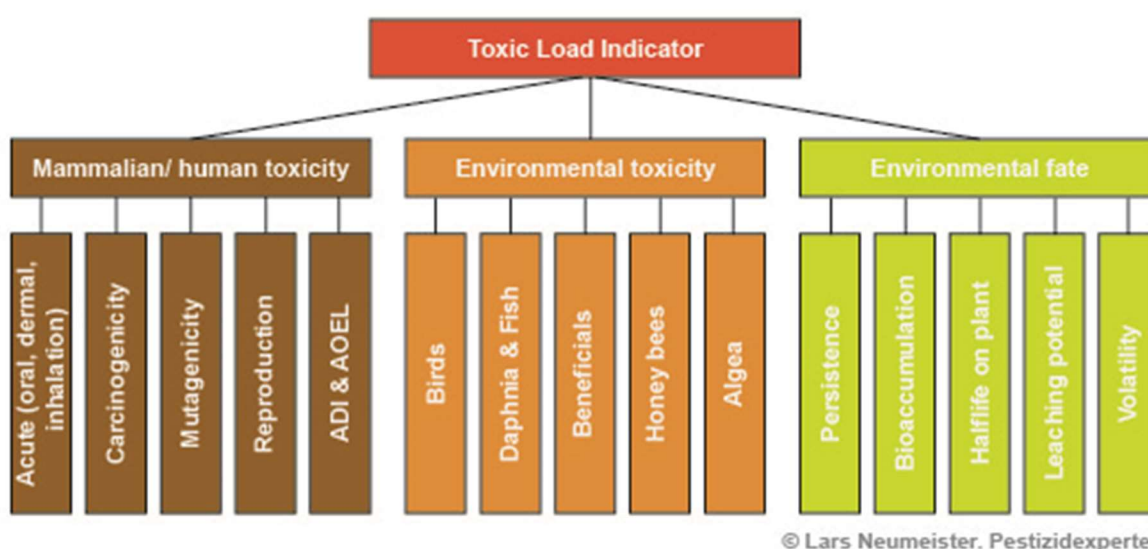
For the toxic load model, three different categories have been put together in order to cover

- a) Toxicity for Humans (mammals),
- b) Environmental toxicity and
- c) Environmental Fate and Transport (Exposure Probability)

A set of parameters has been assigned to each category. Human toxicity categories cover both acute risks for intoxication and long-term severe or irreversible effects. The environmental toxicity category covers different indicators for terrestrial and aquatic species. The exposition probability comprises risks for humans and the environment, again covering both immediate and potential long-term effects.

An overview of the parameter sets is given in figure 1. The annex gives a detailed overview of the parameters, sources for data and scores for the different hazard levels.

Figure 1: Overview of toxicity parameters of the Toxic Load Indicator (TLI)



The TLI can be described in brief as a qualitative indicator for pesticide active ingredients which translates numerical and non-numerical values (toxicological endpoints, classifications) into a scoring system and which is applied to pesticide use data to measure and compare pesticide use (current use and trends). The developed indicator differs from existing evaluation systems. The major advantage of the TLI is its design as an “open source” scoring system, which makes different pesticides properties transparent and more understandable. It is described in detail and the primary data sources are publicly available and free of cost.

Table 1: Overview of the scoring system

	Data basis for scoring	Ranking procedure
Human Toxicity		
Acute Toxicity (Oral, dermal, inhalation)	GHS Acute toxicity category	WHO and GHS classification are treated equally. The rating indicating the highest toxicity determines the score. When WHO or GHS classification do not exist LD50 values from authorization data are used.
	WHO Recommendation	
	Acute LD50	
Carcinogenicity	GHS	The highest toxicity ranking of any of the three databases determines the TLI score
	IARC	
	US EPA Cancer classification	
Mutagenicity	GHS	As categorized; details see Annex
Reproductive & developmental toxicity	GHS	As categorized; details see Annex
Acceptable Daily Intake (ADI) & Acceptable Operator Exposure Level (AOEL)	EU Pesticide Database	As categorized; details see Annex The higher toxicity determines the TLI score.
Environmental Toxicity		
Algae (Acute EC50 up to 96 h (growth))	Footprint classification	As categorized; details see Annex
Waterflea (Daphnia) & Fish (Acute LC50 up to 96h)	US EPA ecotoxicity categories	As categorized; details see Annex
Birds (Acute LD50 up to 96h)	US EPA ecotoxicity categories	As categorized; details see Annex
Beneficial organisms (Lethal rate (50%))	Maximum LR50 in 20 Percentile or Footprint classification	As categorized; details see Annex
Honey bees (acute LD50 per bee)	US EPA ecotoxicity categories	As categorized; details see Annex
Exposure Probability		
Bioconcentration factor (BCF); log KOW P	Footprint classification	As categorized; details see Annex
Persistence in soils, sediments and water	Footprint classification	As categorized; details see Annex
Leaching potential	Footprint classification	As categorized; details see Annex
Volatility	Footprint classification	As categorized; details see Annex
Half-life on plant	Fantke P, Juraske R (2013)	As categorized; details see Annex

Source: Summary of Annex

1.2 Description of parameters

1.2.1 Mammalian (human) toxicity

1.2.1.1 Acute toxicity

The acute toxicity describes the adverse effects of a substance that result either from a single exposure or from multiple exposures in a short time span (usually less than 24 hours). To be described as acutely toxic, the adverse effects should occur within 14 days of the administration of the substance depending on the species.

The acute toxicity usually expressed as LD50 (lethal dose for 50% of a test population) in mg/kg body weight. The test species representing mammals are usually rats, but also other mammalian species are used. LD50 tests are relatively simple and do not leave much room for interpretation, therefore, for all pesticides LD50 values for mammals are available. The age of the data does not reflect the quality, since uniform testing guidelines have been in place for a long time.

Exposure to pesticides can occur orally or dermally or via inhalation. Dermal exposure is most common during the occupational use of pesticides. LD50 values vary depending on the path of exposure and the physical state of the substance (solid, liquid, gas, dust etc.).

For the TLI, the four GHS Acute Toxicity categories 1-4 and the five WHO classes Ia – “U” (“Extremely hazardous”-“Unlikely to present harm”) are used, Category 1/Ia reflecting the highest toxicity. The GHS Acute Toxicity category considers all possible exposure paths and physical states. The WHO considers only oral and dermal exposure.

The classification by GHS or the WHO/IPCS recommended classification of pesticides by hazard is applied for deriving a score (a higher rating supersedes lower rating). If both sources do not contain a classification, the LD50 values for the specific pesticide are identified and ranked according to the GHS acute toxicity categories.

It should be noted that the GHS as well as the WHO present, in some cases, a gross underestimation of the real risk for humans (see Dawson et al. 2010)⁵. Pesticides with the highest human fatality rates: Paraquat dichloride and Endosulfan (ibid.) are neither rated as “*Fatal if swallowed*” nor “*Highly or extremely hazardous*” by GHS resp. WHO. For the purpose of the TLI, that underestimation plays no role, but if the TLI were used for the identification of priority pesticides (e.g. for a phase out), the real human toxicity should be better reflected.

1.2.1.2 Carcinogenicity, Mutagenicity and Reproductive and Developmental Toxicity (CMR)

Carcinogenicity, mutagenicity and reproductive and developmental toxicity present severe and often irreversible effects causing extreme suffering and may have fatal consequences. In the case of mutagenicity, also “genotoxicity” implies, with potentially heritable damages.

The investigation of carcinogenicity, mutagenicity and reproductive and developmental toxicity (CMR) is therefore part of the pesticide authorization process.⁶ For that purpose, long-term studies (1-2 years) are conducted and specific endpoints are observed. Test species are commonly rats, mice and dogs.

Several systems for the classification of **carcinogenicity** of pesticides exist, but the US EPA, GHS and IARC classifications are most commonly applied. The GHS carcinogenicity classification is used by the

⁵ Dawson AH, Eddleston M, Senarathna L, Mohamed F, Gawarammana I, Bowe SJ, Manuweera G, Buckley NA (2010): Acute Human Lethal Toxicity of Agricultural Pesticides: A Prospective Cohort Study. PLoS Medicine 7(10): e1000357.

⁶ More information: <http://www.oecd.org/env/ehs/testing/oecdguidelinesforthetestingofchemicals.htm>

FAO to identify “highly hazardous pesticides”⁷, and the EU uses it for excluding certain substances from authorization.

For the TLI, the US EPA, GHS and IARC carcinogenicity classifications are used in the way that the highest rating among the three determines the score, even if two other organizations rank the pesticide to a lower risk category.

Regarding **mutagenicity** and **reproductive & developmental toxicity** only the GHS classification and the EU classification according to Directive 67/548/EC exist. The latter has been repealed by the so-called GHS regulation 1272/2008/EC. Therefore, the GHS classification system is used for the TLI.

1.2.1.3 Acceptable Operator Exposure Level (AOEL) and Acceptable Daily Intake (ADI)

The AOEL (Acceptable Operator Exposure Level) as an occupational limit value for hazardous substances and is considered a valuable source of information for the TLI reflecting **chronic toxicity**. The AOEL is a health-based limit-value that represents the maximum amount of active substance to which the operator or bystanders may be exposed without any adverse health effect. It is expressed as an internal level (in milligrams/kilograms body weight/day)⁸. However, AOEL values are only available for a limited number of pesticides.

Therefore, the Acceptable Daily Intake (ADI) is used as additional source to reflect chronic toxicity. The ADI as defined by WHO⁹, is a measure of the amount of a specific substance in food or drinking water that can be ingested (orally) on a daily basis over a lifetime without an appreciable health risk. ADIs are expressed usually in milligrams (of the substance) per kilograms of body weight per day. ADI values are widely available for most pesticides.

The ADI is similar to AOEL based on “No Observed Adverse Effect Levels” (NOAEL) that result from long-term studies. The lower the NOAEL, the higher the potential chronic toxicity is. For each pesticide, numerous “No Observed Adverse Effect Levels” (NOAEL) exist, depending on the type of study and the observed endpoint. The ADI is derived from the most relevant effect at the lowest dose.

With regard to insecticides, the ADI often reflects **neurological effects**, which are otherwise hardly reflected in commonly used classification systems. For example, the neonicotinoid insecticides Imidacloprid and Acetamiprid have relatively low scores in the TLI parameters for acute toxicity and CMR. However, these two substances are identified neuro-developmental toxins (EFSA 2013). The ADI scoring within the TLI reflects this.

A unique analysis¹⁰ of available EU data indicated that a good correlation between ADI and AOEL values exists (correlation co-efficient: 0.76). The EU Pesticide Database also shows that only 24.7% of AOEL values are lower than the ADI, i.e. indicating an increased sensitivity.

⁷ For more information see FAO (n.d.): AGP –Highly Hazardous Pesticides at <http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/code/hhp/zh/>

⁸ De Heer C et al (2007): Special tool: acceptable operator exposure level (AOEL). <http://www.baua.de/cae/servlet/contentblob/676686/publicationFile/>

⁹ WHO (1987): Principles for the safety assessment of food additives and contaminants in food. Environmental Health Criteria 70. <http://www.inchem.org/documents/ehc/ehc/ehc70.htm>

¹⁰ Comparison done 30.06.2016

For the TLI, the ADI or the AOEL values as published in the EU pesticides database¹¹ are used as a primary source. For pesticides where both values exist (ADI and AOEL), the lower, i.e. the more sensitive value, prevails.

1.2.2 Environmental toxicity

1.2.2.1 5 parameters for terrestrial and aquatic species

Five different species or species groups are covered under environmental toxicity presenting terrestrial and aquatic species across the food web and/or of (agro-)ecological importance (bees and beneficial organisms):

1. Algae
2. Waterfleas (*Daphnia spec.*) or Fish
3. Birds
4. Beneficial organisms (arthropods important for natural/biological control)
5. Honey bees

The rather high number of species (groups) is regarded as necessary to reflect the toxicity of a pesticide appropriately. In order to potentially reduce the number of species, it was attempted to identify species or species groups¹², which could represent others. However, among the selected species, there was no substantial evidence to support the idea of one representative species or species group. There was either no correlation between the acute toxicity for the different species or the database was too small:

- A strong correlation exists between *Daphnia* species (mostly *Daphnia magna*) and fish species (mostly rainbow trout [*Oncorhynchus mykiss*] with a correlation co-efficient of 0,89 (n=363¹³);
- Another strong correlation was identified between bird toxicity (mostly *Colinus virginianus*) and *Daphnia* species (mostly *Daphnia magna*) with a correlation co-efficient of 0,98 (n=93¹⁴). However, it needs to be taken into account that the number of comparable values is rather small.
- No correlation seems to exist between the toxicity to honey bees and toxicity to *Daphnia*. The correlation co-efficient is basically zero (n=368¹⁵).
- No correlation seems to exist between the toxicity to honey bees and toxicity to beneficial organisms. The correlation co-efficient is low 0,26 (n=54¹⁶) but the number of comparable values is rather small.

¹¹ See http://ec.europa.eu/sanco_pesticides/public/index.cfm

¹² Absolute LC50/LD50 values (no ">" "<" operators) from the footprint data were correlated with each other and the correlation co-efficient determined.

¹³ Absolute LC50 data (no ">" "<" operators) from Footprint Database. Only values derived from regulatory assessment were used.

¹⁴ Absolute LC50 data (no ">" "<" operators) from Footprint Database. Only values derived from regulatory assessments were used.

¹⁵ Absolute LC50 data (no ">" "<" operators) from Footprint Database, all sources.

¹⁶ Absolute LC50 data (no ">" "<" operators) from Footprint Database, all sources.

Except for the natural enemies (beneficial organisms), acute toxicity data (LC/EC/LD exposure time up to 96 hours) are used for the TLI. The ranking is either taken from the US EPA Ecotoxicity Categories for Terrestrial and Aquatic Organisms (US EPA 2016)¹⁷ or the Footprint Database¹⁸. For the beneficial organisms several types of values exist in the footprint database for mostly two main indicator species (the parasitic wasp *Aphidius rhopalosiphi* and the predatory mite *Typhlodromus pyri*): the lethal rate (50%) in g/ha, the percentage of a certain effect (mostly % mortality) and non-numerical values such as “Harmful” or “Harmless”.

In order to come up with a meaningful ranking for the lethal rate (50%) in g/ha, the available data were sorted ascending per species and the number of records divided by the number of intended ranks (five). Basically, that means that the sorted data are divided in 5 percentiles (20, 40, 60, 80, 100) and the highest values within each percentile determines the threshold for the score.

Due to the strong correlation, Daphnia and Fish toxicity are evaluated in one score, where the highest rating determines the score.

1.2.2 Environmental fate and transport (exposure probability)

Five key parameters are covered under environmental fate and transport presenting terrestrial, aquatic and aerial transport and fate in different environments.

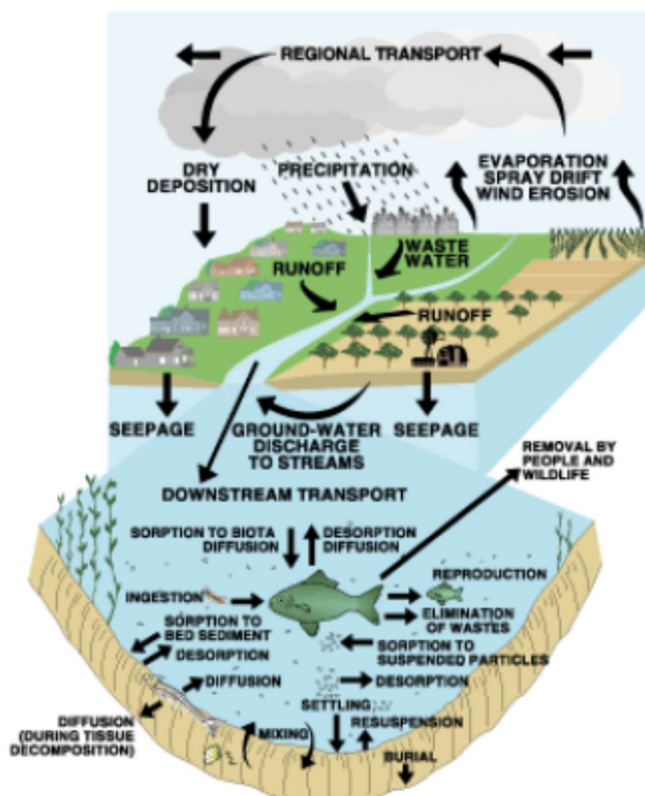
1. Bioconcentration factor or log KOW P
2. Persistence in soil, water and sediments (half-life)
3. Persistence on the plant (half-life)
4. Volatility (vapour pressure)
5. Leaching potential

Figure 2 illustrates how pesticides can move through the environment. Transport depends on physical properties of the chemical, but also on environmental conditions like carbon content of soils, precipitation, erosion and temperature and many other factors.

¹⁷ Ecotoxicity Categories for Terrestrial and Aquatic Organisms: <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/technical-overview-ecological-risk-assessment-0>

¹⁸ <http://sitem.herts.ac.uk/aeru/ppdb/en/index.htm>

Figure 2: Environmental transport model



Source: USGS (United States Geological Survey)

A pesticide which has a high **Bioconcentration factor** or log KOW P is very likely to accumulate in the tissue of organisms – usually the Bioconcentration factor is derived from tests with fish, but terrestrial accumulation is possible as well¹⁹ – that means the pesticide is transported with that animal and possibly accumulated through the food web.

The OSPAR convention as well as the GHS²⁰ identified a threshold of 500 for a BCF for bioaccumulative respectively chronically (long-term) hazardous pesticides to aquatic species – this threshold is used in the TLI for the highest score. When no BCF value is available the log KOW P is used, which commonly serves as a trigger value (Kelly et al. 2007).

Persistence describes typically how fast a pesticide degrades in different environments – the longer it persists, the higher the likelihood of further transport e.g. through erosion and or exposure of non-target organisms or humans. For the TLI, the scoring system differs for each represented environmental medium (soil, water, sediment, plant), with the half-life in days being the indicator. For soil, water, sediment the half-lives are aggregated and higher values supersede lower values. Persistence in the air cannot be reflected properly, because of a lack of data.

Pesticide are eventually degraded into elements or into stable natural compounds like CO₂. Elements²¹ used as pesticides already present the final stage of a degradation process. They cannot degrade

¹⁹ Kelly BC, Ikonomou MG, Blair JD, Morin AE & Gobas FAPC (2007): Food Web-Specific Biomagnification of Persistent Organic Pollutants. Science 318(5847):44.

²⁰ See Table 4.1.0 in regulation 1272/2008/EC

²¹ Only Sulfur is relevant here.

further and although they are *per se* persistent, they cannot be evaluated as persistent pesticides. The TLI scoring reflects elements therefore differently.

The **volatility** is a measure for evaporation and drift of pesticides; some pesticides easily evaporate from the plant surface or the soils, drift away and potentially damage non-target organisms or humans²². The Australian Government recently banned²³ certain highly volatile 2,4-D esters/salts because they can drift (after evaporation) over 50 km away and damage non-target organisms. For the TLI the vapour pressure is used as an indicator for volatility. While other indicators exist (Henry Law Constant, boiling point), they seem not to correlate to each other. For the development of the ranking the vapour pressure range suggested by PAN North America is used (Hill et al. n.d)²⁴. The ranking suggested by the Footprint Database is not differentiated enough and would lead to a highest score for most pesticides.

Leaching potential is mostly a result of adsorption and persistence. Adsorption indicates how strongly a chemical binds to the soil (carbon containing matter) while moving down with water. A pesticide that does not adsorb to soil, but has a long persistence is a candidate for leaching. The importance of adsorption and persistence can be illustrated through the Groundwater Ubiquity Score (GUS) index. GUS is calculated using the following simple equation:

$$\text{GUS} = \log(\text{DT}_{50}) \times (4 - \log(\text{K}_{oc}))$$

If GUS is > 2.8, the pesticide may leach easily²⁵, and this figure is used for the highest score for the TLI. If GUS is < 1.8, the pesticide will be classified a "non-leacher". Therefore, GUS indicates the intrinsic mobility of pesticides. Whether or not leaching occurs, depends on environmental conditions and the amounts and frequency the pesticide used.

2 Scoring System

A scoring system was developed that relates the highest toxicity resp. the strongest effect to the highest score, the lowest toxicity resp. the weakest effect to the lowest score. The scale ranges from 1 point to 10 points for the highest toxicity/strongest effect, with five different grades in the order 1-2-5-8-10. A score of five always is used in case no data for the specific parameter is available (default value). The lowest possible score is 15 = 15 parameters x lowest score 1. The highest possible score for an individual pesticide is commonly 150 = 15 parameters x highest score 10.

Basis for the scoring are existing classifications by the WHO, GHS, the US EPA or classifications suggested by the Footprint Database Project. Detailed scores and referenced classification systems and/or limit values are outlined in the annex. In general, for numerical data with a normal distribution a breakdown in five percentiles is also possible. However, for the Toxic Load Indicator, the highest score of ten usually relates to a certain classification threshold.

²² http://www.panna.org/legacy/panups/panup_20030509.dv.html

²³ <http://apvma.gov.au/node/12351>

²⁴ agis.ucdavis.edu/pur/pdf/AirPic_42007.pdf

²⁵ <http://www.pw.ucr.edu/textfiles/PesticideWiseWinter2002.htm>

In case the reference data for the TLI Scores (e.g. LD50; LC50, EC50 values) meet the exact threshold for a specific rank and have operators (“<” or “>”) assigned, the higher resp. lower score is used for the assessment.

The annex gives a detailed overview of the parameters, sources for data and scores for the different hazard levels.

For a better understanding, Tables 2 and 3 illustrate for the parameter “ecological toxicity to birds” how toxicological endpoints (lethal dose [LD] or lethal concentration [LC] for 50% of the population) translate into TLI scores assigned to each value for a sample of 10 active ingredients.

Table 2: Acute Toxicity Birds

LD50 (oral)	US EPA ‘narrative’	TLI Score
≤ 10	very highly toxic	10
> 10 to ≤ 50	highly toxic	8
>50 to ≤ 500	moderately toxic	5
> 500 to ≤ 2000	slightly toxic	2
> 2000	practically nontoxic	1
Active ingredients without data		5

Source: cf. Annex Scoring System

Table 3: Translation of toxicological endpoints to TLI scores for a sample of 10 active ingredients

Active Ingredient	Bird LD 50 (mg/kg)	Classification range	TLI Score
2,4-D	>500	> 500 to ≤ 2000	2
Acetamiprid	98	>50 to ≤ 500	5
Chlorpyrifos	13,3	> 10 to ≤ 50	8
Dimethoate	10,5	> 10 to ≤ 50	8
Fipronil	11,3	> 10 to ≤ 50	8
Glyphosate	>2000	> 2000	1
Imidacloprid	31	> 10 to ≤ 50	8
Mancozeb	>2000	> 2000	1
Pendimethalin	1421	> 500 to ≤ 2000	2
Teflubenzuron	>2250	> 2000	1

Source: Pesticide Database of Lars Neumeister

Figure 3 illustrates the TLI scoring for four eco-toxicological parameters for a sample of 10 active ingredients. It shows several endpoints (lethal dose [LD] or lethal concentration [LD] for 50% of the population) and the TLI scores assigned to each value. Individual data for daphnia and fish are combined in a single joint score.

3 Weighting

The final TLI Score does not include any default weighting: the sums of the parameter groups are simply added to determine the total score.

However, when calculating the Toxic Load per area, certain scenarios are not reflected, for example if pesticide spraying is outsourced or “spray groups” exist. The employees of pest control service companies as well as on-farm spray groups often apply pesticides very frequently, sometimes every day for several hours. A Toxic Load per area unit therefore underestimates that potential exposure scenario. In projects²⁶ where the TLI Method is currently used, the Health Score (Mammalian toxicity) is therefore doubled. However, weighting of parameter groups can be decided upon individually, e.g. by Sustainability Standards or On-Farm Projects, according to their particular situation or priorities.

Figure 4 gives an example for 10 pesticides with a weighting factor of 2 for the mammalian toxicity.

Figure 3: TLI Scoring for a sample of ten active ingredients

Toxic Load Indicator		Mammal toxicity						Environmental Toxicity					Environmental Fate and Transport									
Active Ingredient	Total Score	WF	SUM1	Acute Tox.	Carcinogenicity	Repro. Tox.	Mutagenicity	AOEL /ADI	WF	SUM 2	Algae	Daphnia/Fish	Birds	Bee	Beneficial	WF	SUM 3	Bioaccumulation	Persistence	Half life on plant	Leaching Pot.	Volatility
1 Bifenthrin	129.0	2	56.0	8	8	1	1	10	1	37.0	5	10	2	10	10	1	36.0	10	10	10	1	5
2 Ethoprophos	124.0	2	64.0	10	10	1	1	10	1	34.0	1	8	10	5	10	1	26.0	2	8	1	5	10
3 Fipronil	123.0	2	50.0	5	8	1	1	10	1	41.0	5	8	8	10	10	1	32.0	5	10	10	5	2
4 Carbendazim	119.0	2	74.0	1	8	10	10	8	1	23.0	5	8	1	1	8	1	22.0	1	1	10	5	5
5 Diazinon	118.0	2	48.0	2	10	1	1	10	1	45.0	5	10	10	10	10	1	25.0	10	1	5	1	8
6 Fenamiphos	115.0	2	42.0	8	1	1	1	10	1	45.0	5	10	10	10	10	1	28.0	1	2	10	10	5
7 Linuron	114.0	2	62.0	2	8	10	1	10	1	29.0	5	8	5	1	10	1	23.0	1	8	1	5	8
8 Lambda-cyhalothrin	114.0	2	50.0	8	5	1	1	10	1	36.0	5	10	1	10	10	1	28.0	10	10	5	1	2
9 Abamectin	112.0	2	60.0	10	1	8	1	10	1	26.0	5	10	5	1	5	1	26.0	1	8	10	5	2
10 Chlorpyrifos	109.0	2	36.0	5	1	1	1	10	1	43.0	5	10	8	10	10	1	30.0	10	1	10	1	8

Yellow numbers = average score for datagaps
WF: Weighting Factor

* Pesticides: 10

Source: Pesticide Database of Lars Neumeister

4 Data availability and updated requirements

4.1 Availability of scientific data for active ingredients

All synthetic active ingredients can be assessed for their TLI score, since data gaps are reflected in the scoring system by the default value of 5. Most pesticides used in cotton are or were authorized in the EU or the USA and assessment reports, which include necessary data and are available and found in publicly available databases.

The scoring system is not suitable for “natural” compounds used as plant protection products, which do not require authorization or full testing. Some of these compounds (e.g. *Bacillus thuringiensis*, pheromones) are defined as “low risk substances”. EU Commission Regulation (EC) No 1095/2007 (4) as well as Annex II of Regulation 1107/2009/EC define criteria for such low risk

²⁶ e.g. the WWF/EDEKA/Dole Banana project in Ecuador/Colombia; Fair’n Green Vineyards in Germany

substances. Such natural compound pesticides, which have been authorized in the EU because they meet the EC 'low risk' criteria receive a default total score of 15 – the lowest possible total score.

4.2 New scientific findings - Requirements for Updates on active ingredient scores

Since scores for the different parameters are most times drawn from data provided during the registration process, most data do not change much once an active ingredient is registered or classified.

However, a regular check of primary classification systems used for TLI is needed:

- IARC and US EPA review their cancer classification regularly and this may have consequences for the scores of certain substances,
- The European Chemical Agency (ECHA)²⁷ responsible for the EU GHS frequently (2-3 per year) amends classifications for the purposes of adaptation to technical and scientific progress. In general, these adaptations are only applied to new substances submitted for authorization. Previously done GHS entries remain (mostly) unchanged,
- The scoring for plant half-life is based on a literature review and new chemicals, not covered by the review have to be evaluated individually.

4.3 Pesticide use data

Once the comprehensive Toxic Load Indicator has been compiled, the Toxic Load per area can be calculated. To come up with a robust and meaningful calculation, proper pesticide use reporting is an essential prerequisite. Incorrect reporting can lead to wrong calculations of the toxic load and wrong interpretation.

In global cotton production, the type of pesticide users varies from large, highly advanced and mechanized farms to illiterate smallholders. A pesticide use reporting system adjusted to the ability of the pesticide users is required, and responsibilities must be shared. In the end, the identity of the active ingredients used and the amounts used per active ingredient and area are necessary for the Toxic Load calculation.

Basis for any use reporting system is usually the amount per product used, and ideally, the identity of each pesticide product must be checked using the Material Safety and Datasheets (MSDS) and/or by sources from the regulatory authorities. If they are not available photos of the product labels should be filed.

Invoices for on-farm deliveries must be kept and amounts per product purchased should be entered in a booking system. The pesticide storage place needs a log book, which registers how much of each product was stored at what date, and how much was taken out for treatments. Finally, site specific spray records must be kept, where the amount of product per area is recorded. The invoices, the storage log-book and the spray records must be frequently checked for consistency. Where third parties conduct spray operations the invoices, containing all details (date of treatment, area treated, amount applied, pest controlled etc.) of these companies serve as a base to the calculation of the pesticide use.

²⁷ <http://echa.europa.eu/regulations/clp>

The use of a product must be converted in use by active ingredient(s). The label, the MSDS or authorization data must be used to identify the active ingredient and the concentration. Some products contain a salt or ester of an active ingredient and the concentration is expressed as salt/ester and/or as pure substance. It must be clear to what the concentration refers to.

5 TLI methodology: Advantages and Limitations

There are a number of benefits connected to the TLI methodology, but like every other methodology, it also has limitations which need to be considered.

Its benefits can be summarized as follows:

Using the TLI methodology will **increase the understanding about potential hazards** presented by pesticide use. The calculated toxic load gives a **quick, but comprehensive indication for potential hotspots and potential problems** in the field. By comparing farms with each other “outliers” and “best performers” can be rather easily identified.

The results of the 1-10 **ranking for active ingredients can be understood by laypeople** in NGOs, certification schemes and trade companies, who usually do not deal with toxicological endpoints and their interpretation.

The scoring of active ingredients and the **calculation of toxic load indicates potential hazards** and this will **foster and facilitate informed decision making** in the selection of pest control measures. Furthermore, a prognosis how the Toxic Load will develop in pesticide use reduction programs helps to prevent unwanted substitution effects. TLI prognosis before implementing such a programme will help identify and therefore avoid situations where problematic pesticides, for example, with acute mammalian toxicity concern, are replaced with others that presents chronic hazards.

However, several limitations have to be taken into account:

The TLI is a database derived indicator intended to better present specific pesticide properties and to identify potential hazards to pesticide users and the environment when combined with use data. So far, a validation as to whether or not a high toxic load is associated with actual adverse effects in the field (and vice versa) has not been conducted. That should be undertaken and field indicators for verification need to be developed.

The TLI scores are based on a limited number of parameters. Certain effects such as endocrine disruption are not directly covered, because standardized methods for the identification of endocrine disrupting chemicals are not finalized, and thus no up-to-date reference list exists. However, scientific evidence suggests that chemicals which show carcinogenic properties AND reproductive toxicity are at the same time endocrine disrupters. The TLI reflects carcinogenic properties and reproductive toxicity and therefore includes, at least partly, potential endocrine disrupters.

Data for the environmental toxicity are based on endpoints for acute toxicity for a limited number of species. These species might not be the most sensitive species. *Daphnia magna* as a standard test species for aquatic toxicity for example seems to be particularly insensitive against neonicotinoids, which show high toxicity to other aquatic invertebrates (Morissey et al. 2015).

Prabhaker et al. (2007 & 2011) tested the acute toxicity of nine insecticides to four parasitoid species, and it seems the toxicity is species and pesticide specific. They found that toxicity to the most sensitive

species to the most insensitive species can vary by a factor over 20,000, and a pesticide with lower toxicity to three parasitoids can show very high toxicity to the fourth. In pesticide use reduction projects, which aim to enhance natural biological control, the specific beneficial fauna has to be monitored and evaluated for sensitivity to pesticides.

The TLI and the Toxic Load are calculated for active ingredients and their usage (amount of active ingredient used per area). Working on an international scale, a more precise approach which looks at overall product toxicity is considered almost impossible. While the active ingredient is usually the effective (and most toxic) compound in a pesticide product, adjuvants added to the tank or “inert²⁸” ingredient can enhance toxicity and change environmental behavior. Bonmatin et al. (2015) showed that commercial formulations may contain inerts that increase the solubility of the active substance, and one research group consistently found commercial pesticides products to have a higher leaching potential than the actual active ingredient (ibid. see also Krogh et al. 2003).

Use of high volume pesticides with relatively low TLI scores (e.g. sulphur or sodium hydrogen carbonate in vineyard, orchards) distorts the toxic load per area. The high amounts used “overwrite” the score, but these are single cases and it is recommended to conduct Toxic Load calculation with as well as without these compounds. Another possibility to enhance the visibility of the toxicity is to give more weight (factor x TLI Score) to the TLI Score than to the amounts used.

²⁸ “Inert Ingredients” are for example: solvents, surfactants, and emulsifiers having a big variety of functions like preventing caking or foaming, extending product shelf-life, or allowing herbicides to penetrate plants with the general aim to maintain and enhance the effect of the active ingredient.

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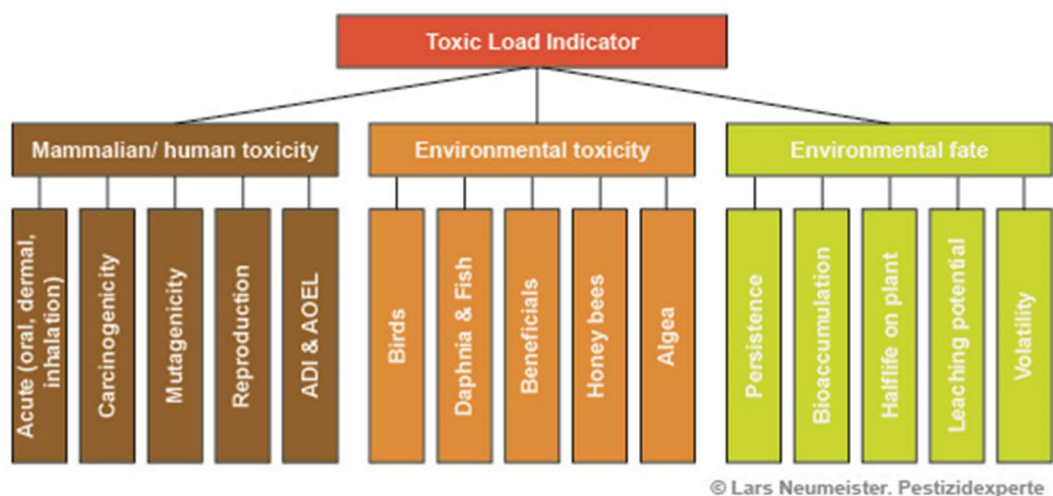
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Annex: Scoring System

Graphical Overview



Mammalian toxicity

Acute Toxicity Score

All Exp.	Oral		Inhalation			
GHS Acute Cat.	WHO*	LD50	Gases (ppm/V)	Vapours (mg/l)	Dusts and Mists (mg/l)	Score
1	Ia	≤ 5	LD50 ≤ 100	LD50 ≤ 0,5	LD50 ≤ 0,05	10
2	Ib	5 < LD50 ≤ 50	100 < LD50 ≤ 500	0,5 < LD50 ≤ 2	0,05 < LD50 ≤ 0,5	8
3	II	50 < LD50 ≤ 300	500 < LD50 ≤ 2500	2 < LD50 ≤ 10	0,5 < LD50 ≤ 1	5
4	III	300 < LD ≤ 2000	2500 < LD50 ≤ 2000	10 < LD50 ≤ 20	1 < LD50 ≤ 5	2
**	U	>2000	>2000	>20	>5	1
Active ingredients without data						5

**Active ingredients evaluated by GHS Regulation and not classified in any acute toxicity category.

*The WHO Classification includes dermal toxicity, if higher than oral toxicity.

Values with grey background are only applied, when GHS or WHO classification is not available.

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Carcinogenicity Classification and Scoring

GHS Classification	EPA Classification – 2005	EPA Classification – 1999 Draft	EPA Classification – 1996	EPA 1986 Classification	Cancer Classification of the IARC	Score
Known human carcinogens' (Category 1A)	Carcinogenic to humans.	Carcinogenic to humans.	Known/Likely	Human carcinogen	Group 1 The agent (mixture) is carcinogenic to humans.	10
Presumed human carcinogens' (Category 1B)	Likely to be carcinogenic to humans.	Likely to be carcinogenic to humans.		Group B – Probable human carcinogen Group B1 is reserved for agents for which there is limited evidence of carcinogenicity from epidemiologic studies Group B2 is used for Agents for which there is "sufficient: evidence from animal studies and for which there is "inadequate evidence" or "no data" from epidemiologic studies.	Group 2A The agent (mixture) is probably carcinogenic to humans.	10
Suspected human carcinogens (Category 2)	Suggestive evidence of carcinogenic potential	Suggestive evidence of carcinogenicity but not sufficient to assess human carcinogenic potential		Group C – Possible human carcinogen	Group 2B The agent (mixture) is possibly carcinogenic to humans.	8

GHS Classification	EPA Classification – 2005	EPA Classification – 1999 Draft	EPA Classification – 1996	EPA 1986 Classification	Cancer Classification of the IARC	Score
	Inadequate information to assess of carcinogenic potential	Data are inadequate for an assessment of human carcinogenic potential	Cannot be determined	Group D – Not classifiable as to human carcinogenicity	Group 3 The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans.	5
Active ingredients evaluated by GHS Regulation 1272/2008/EC and not classified in any carcinogenicity category.	Not Likely to be carcinogenic to humans	Not Likely to be carcinogenic to humans.	Not likely	Group E – Evidence of non-carcinogenicity	Group 4 The agent (mixture) is probably not carcinogenic to humans.	1
Active ingredients without data						5

Primary Sources:

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Mutagenicity

GHS	Description	Score
Category 1A	The classification in Category 1A is based on positive evidence from human epidemiological studies. Substances to be regarded as if they induce heritable mutations in the germ cells of humans.	10
Category 1B	The classification in Category 1B is based on: — positive result(s) from in vivo heritable germ cell mutagenicity tests in mammals; or — positive result(s) from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to derive this supporting evidence from mutagenicity/genotoxicity tests in germ cells in vivo, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or — positive results from tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.	10
Category 2	substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans	8
	Active ingredients evaluated by GHS Regulation 1272/2008/EC and not classified in any mutagenicity category.	1
Active ingredients without data		5

Primary Sources:

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Reproductive and developmental toxicity

GHS	Description	Score
Category 1A	Known human reproductive toxicant The classification of a substance in Category 1A is largely based on evidence from humans.	10
Category 1B	Presumed human reproductive toxicant The classification of a substance in Category 1B is largely based on data from animal studies.	10
Category 2	Suspected human reproductive toxicant Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information.	8
	Active ingredients evaluated by GHS Regulation and not classified in any category for reproductive toxicity.	1
	Active ingredients without data	5

Primary Sources:

EC (2008): Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labeling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. Official Journal of the European Union L 353/1 and its amendments

AOEL/ADI (Acceptable Operator Exposure Level/Acceptable Daily Intake)

AOEL/ADI-Wert [mg/kg body weight]	Score
AOEL/ADI < 0,01	10
0,01 ≤ AOEL/ADI < 0,1	8
0,1 ≤ AOEL/ADI < 1	5
1 ≤ AOEL/ADI < 10	2
AOEL/ADI ≥ 10 or "not appl." or "n.n."	1
Active ingredients without data	5

Primary Source:

EC (n.d.): EU Pesticides database. European Commission. <http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=activesubstance.selection&language=EN>

Environmental toxicity

Acute toxicity Algae

EC50 (growth) mg/l (ppm)	Footprint 'narrative'	Score
≤ 0,01	Highly toxic	10
> 0,01 - ≤ 10	Moderately toxic	5
>10	Low toxicity	1
Active ingredients without data		5

Primary Source:

FOOTPRINT (n.d.): The FOOTPRINT Pesticide Properties DataBase. Database collated by the University of Hertfordshire as part of the EU-funded FOOTPRINT project (FP6-SSP-022704): <http://sitem.herts.ac.uk/aeru/iupac/>

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University of Hertfordshire (n.d.): The Veterinary Substance Database (VSDB) developed by the Agriculture & Environment Research Unit (AERU), University of Hertfordshire, 2011-2016

Secondary Source:

BCPC (n.d.): Online Pesticide Manual of the British Crop Protection Council (BCPC): <http://bcpcdata.com/pesticide-manual.html>

Acute toxicity Daphnia and Fish

LC50/EC50 (acute) mg/l (ppm)	US EPA 'narrative'	Score
≤ 0,1	very highly toxic	10
> 0,1 - ≤ 1	highly toxic	8
>1 - ≤ 10	moderately toxic	5
> 10 - ≤ 100	slightly toxic	2
> 100	practically nontoxic	1
Active ingredients without data	-	5

Primary Source:

FOOTPRINT (n.d.): The FOOTPRINT Pesticide Properties DataBase. Database collated by the University of Hertfordshire as part of the EU-funded FOOTPRINT project (FP6-SSP-022704): <http://sitem.herts.ac.uk/aeru/iupac/>

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University of Hertfordshire (n.d.): The Veterinary Substance Database (VSDB) developed by the Agriculture & Environment Research Unit (AERU), University of Hertfordshire, 2011-2016

Secondary Source:

BCPC (n.d.): Online Pesticide Manual of the British Crop Protection Council (BCPC): <http://bcpcdata.com/pesticide-manual.html>

Acute toxicity birds

LD50 mg/kg bw (oral)	US EPA 'narrative'	Score
≤ 10	very highly toxic	10
> 10 to ≤ 50	highly toxic	8
>50 to ≤ 500	moderately toxic	5
> 500 to ≤ 2000	slightly toxic	2
> 2000	practically nontoxic	1
Active ingredients without data		5

Primary Source:

FOOTPRINT (n.d.): The FOOTPRINT Pesticide Properties DataBase. Database collated by the University of Hertfordshire as part of the EU-funded FOOTPRINT project (FP6-SSP-022704): <http://sitem.herts.ac.uk/aeru/iupac/>

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Secondary Source:

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Quality Control:

Mineau P, Baril A, Collins BT, Duffe D, Joerman G& Luttk R (2001): Pesticide Acute Toxicity Reference Values for Birds, Rev Environ Contam Toxicol 170:13-74, Springer

Beneficial organisms

Lethal Rate (50%) in g/ha	Percent effect (mortality, beneficial capacity)	Footprint 'narrative'	Score
<5	> 79	Harmful	10
> 5 to ≤ 40	-	-	8
> 40 to ≤ 110	30 - 79	Moderately harmful	5
> 110 to ≤ 500	-	-	2
> 500	< 30	Harmless	1
Active ingredients without data			5
Data for most sensitive species are used for the TLI			

Primary Source:

FOOTPRINT (n.d.): The FOOTPRINT Pesticide Properties DataBase. Database collated by the University of Hertfordshire as part of the EU-funded FOOTPRINT project (FP6-SSP-022704): <http://sitem.herts.ac.uk/aeru/iupac/>

University of Hertfordshire (n.d.): The Bio-Pesticides Database (BPDB) developed by the Agriculture & Environment Research Unit (AERU), University of Hertfordshire, 2011-2016.

University of Hertfordshire (n.d.): The Veterinary Substance Database (VSDB) developed by the Agriculture & Environment Research Unit (AERU), University of Hertfordshire, 2011-2016.

Secondary Source:

BCPC (n.d.): Online Pesticide Manual of the British Crop Protection Council (BCPC): <http://bcpcdata.com/pesticide-manual.html>

Honey bees

Honey bee (<i>Apis mellifera</i>)		
LD50 [µg/bee]	US EPA 'narrative'	Score
< 2	Highly toxic	10
2 – 11	Moderately toxic	5
> 11	Practically nontoxic	1
Active ingredients without data		5

Primary Source:

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Environmental fate and transport

Bioaccumulation

Bioconcentrationfactor (BCF)	LogP KOW	Score*
> 500	>5	10
> 400 - ≤ 500	> 3 - ≤ 5	8
> 300 - ≤ 400	> 2 - ≤ 3	5
> 200 - ≤ 300	> 1 - ≤ 2	2
≤ 200	<1	1
Active ingredients without data		5
*Bioconcentrationfactor (BCF) supersede Log P KOW data		

Primary Sources:

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University of Hertfordshire (n.d.): The Veterinary Substance Database (VSDB) developed by the Agriculture & Environment Research Unit (AERU), University of Hertfordshire, 2011-2016.

Secondary Source (log KOW P):

BCPC (n.d.): Online Pesticide Manual of the British Crop Protection Council (BCPC): <http://bcpcdata.com/pesticide-manual.html>

Persistence in soil, sediments and water

Half-life soil and/or sediment [days]	Half-life in Water [days]	Score
> 90	> 50	10
> 80 ≤ 90	> 40 ≤ 50	8
> 70 ≤ 80	> 30 ≤ 40	5
> 60 ≤ 70	> 20 ≤ 30	2
> 50 ≤ 60	> 10 ≤ 20	1
≤ 50	≤ 10	1
Elements		1
Active ingredients without data		5

Primary Source:

FOOTPRINT (n.d.): The FOOTPRINT Pesticide Properties DataBase. Database collated by the University of Hertfordshire as part of the EU-funded FOOTPRINT project (FP6-SSP-022704): <http://sitem.herts.ac.uk/aeru/iupac/>

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University of Hertfordshire (n.d.): The Veterinary Substance Database (VSDB) developed by the Agriculture & Environment Research Unit (AERU), University of Hertfordshire, 2011-2016.

Secondary Source:

de Blécourt M., Lahr J., van den Brink P.J. (2010): Pesticide use in cotton in Australia, Brazil, India, Turkey and USA, Alterra, Wageningen, 2010. Online available at http://www.icac.org/seep/documents/reports/2010_alterra_report.pdf

Leaching potential

GUS Index (function of soil half-life and soil binding)	Footprint 'narrative'	Score
> 2,8	High leachability	10
2,8 – 1,8	Transition state	5

<1,8	Low leachability	1
Active ingredients without data		5

Primary Source:

FOOTPRINT (n.d.): The FOOTPRINT Pesticide Properties DataBase. Database collated by the University of Hertfordshire as part of the EU-funded FOOTPRINT project (FP6-SSP-022704): <http://sitem.herts.ac.uk/aeru/iupac/>

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Volatility

Vapour pressure (mm HG) at 20-25°C	Score
> 0,01	10
<0,01 to >0,0001	8
<1 x 10 ⁻⁴ - > 1 x 10 ⁻⁶	5
<1 x 10 ⁻⁶ - > 1 x 10 ⁻⁸	2
<1 x 10 ⁻⁸	1
Active ingredients without data	5

Primary Source:

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Secondary Source:

BCPC (n.d.): Online Pesticide Manual of the British Crop Protection Council (BCPC): <http://bcpcdata.com/pesticide-manual.html>

Half-life on plants

Half-life on plant* (days)	Score
> 3,8	10
>1 – <3,8 (or post-emergency herbicide)	5
< 1 (or pre-emergency herbicide)	1
Active ingredients without data	5
*Data for cotton plants are used if available, otherwise averages (per active ingredients) of other available data	

Primary Source:

Fantke P & Juraske R (2013): Variability of Pesticide Dissipation Half-Lives in Plants. Environ. Sci. Technol. (47): 3548–3562. [dx.doi.org/10.1021/es303525x](https://doi.org/10.1021/es303525x)

Scoring for “natural compounds”

Many natural compounds authorized for the use as pesticides were not required to undergo the same risk assessment as synthetic chemicals. In consequence, many data sets needed to derive their TLI Scores are not available. Often natural compounds, such as pheromones, plant extract or oils, organisms/viruses or inorganic substances, are classified as “low risk” pesticides by regulatory authorities.

The term “low risk pesticides” is the short term for pesticides active ingredients which either fulfill the criteria for indications of no harmful effects set by Commission Regulation (EC) No 1095/2007 or meet requirements set in point 5 of Annex II of Regulation (EC) 1107/2009 and which were authorized under the former Directive 91/414/EEC (about 105 pesticides, mainly through Directive 2008/127/EC and 2008/113/EC) or under the current Regulation (EC) No 1107/2009 (five pesticides). With Regulation (EC) No 1107/2009 “Low-risk active substances” became a regulatory term. The TLI methodology does not apply the US EPA definition of “minimum risk pesticides”²⁹ which differs strongly from the EU definition of “low risk pesticides”.

“Low risk” chemicals might be scored with the lowest possible score (15) or lower, when certain risks can be excluded. For substances used in plant protection which are also food/food additives (for example baking powder) a default health score of five might be too high.

²⁹ <https://www.epa.gov/minimum-risk-pesticides/minimum-risk-pesticide-definition-and-product-confirmation>