The user will find here a brief introduction to using the UPERCUT tool. In interpreting the results and their scope, he should also consult the introductory document found on the Website.

An exhaustive description of the rationale and equations used in the development of UPERCUT can be found in the scientific report (in French) and in the scientific journal article (in English) in the Annals of occupational hygiene, also linked on the Website.

The following procedure describes the various steps of how to use UPERCUT, as well as the different types of information and warning messages displayed.

1- Select a chemical

There are 1686 substances in total. Chemicals can be selected using one of the following options:

1- From a drop-down list of CAS numbers in ascending order by clicking on the number of interest. Typing the first, few or all numbers of a particular CAS number of interest will automatically jump to display the possible matching CAS numbers. Click ENTER to select.
2- By manually entering the CAS number, with or without hyphens, in the corresponding textbox then clicking on “Search for a CAS number”.
3- From a drop-down list of substance names arranged in alphabetical order by clicking on the substance of interest. Typing the first, few or all letters of a particular substance name will automatically jump to display the possible matching names. Click ENTER to select.
4- By clicking on “Search in substance names” to manually search for a substance name using the name or part of the name of the substance of interest in the textbox provided. The text entered can be used to search the entire substance list or among previous search results.

2- Information on the chemical substance

Information on the chemical selected is automatically displayed:

1- CAS: the CAS registry number of the substance.

2- Risk phrases: provides risk phrases relevant to dermal risk associated with the selected chemical.

Possible values:

- R21: Harmful in contact with skin
- R24: Toxic in contact with skin
- R27: Very toxic in contact with skin
- R38: Irritating to skin
- R43: May cause sensitization by skin contact
- R66: Repeated exposure may cause skin dryness or cracking
- None: Substance registered without an identified risk phrase
- ---: Substance not registered in with IPCS (International Programme on Chemical Safety).

3- CMR: CMR classification of the substance according to the Annex 1 of the European Union Directive 67/548/EEC.

Possible values:

- C1 or C2 or C3
- M1 or M2 or M3
- R1 or R2 or R3
- None: Substance registered without an identified CMR classification
- ---: Substance not registered

The C, M and R letters stand for:

- Carcinogen (**C**): substances and preparations which, if inhaled, swallowed or absorbed via the skin, may cause cancer or increase its frequency.
- Mutagenic (**M**): substances and preparations which, if inhaled, swallowed or absorbed via the skin, may induce hereditary genetic defects or increase their frequency.
- Toxic to reproduction (**R**): substances and preparations which, if inhaled, swallowed or absorbed via the skin, may induce or increase the frequency of adverse effects in the non-genetic offspring or affect reproductive functions or capacities.

For each C, M or R status, the 3 categories are attributed according to the degree of knowledge and certainty available for the substance or preparation:

- **C**ategory 1: substances and preparations that are known to be CMR to humans (epidemiological data);
- **C**ategory 2: substances and preparations for which there is a strong presumption that human exposure to such substances and preparations may cause or increase the frequency of occurrence of CMR effects mentioned above;
- **C**ategory 3: substances and preparations which cause concern for man owing to possible CMR effects but for which available information is insufficient to classify these substances and preparations in category 2.

4- Skin notation (2010 American Conference of Governmental Industrial Hygienists Threshold limit values):

Possible values:

- Yes: Substance is in the 2010 ACGIH list of TLVs and has been given a skin notation
- No: Substance is in the 2010 ACGIH list of TLVs and has not been given a skin notation
- ---: Substance is not in the 2010 ACGIH list of TLVs

5- Skin notation (2009 Maximal allowable concentration, MAK, values from Deutsche Forshungsgemeinshaft):

Possible values:

- Yes: Substance is in the 2009 list of MAK values and has been given a skin notation
- No: Substance is in the 2009 list of MAK values and has not been given a skin notation
- ---: Substance is not in the 2009 list of MAK values

6- Dermal penetration potential: provides an index of potential for dermal penetration based on values of molecular weight (MW) and octanol/water partition coefficient (logKow).

Possible values:

- Low (MW > 213 & logKow > 1.2)
- Intermediate
- High: (MW $\leq$152 & logKow < 2.6)

3- Animal toxicity (GHS)

Oral and dermal animal toxicity according to criteria by the Globally Harmonized System of classification and labeling of chemicals (GHS) based on the RTECS toxicological data

1- Acute – Skin: in contact with skin
2- Acute – Oral: if swallowed
3- Chronic – Skin: in contact with skin
4- Chronic – Oral: if swallowed

Possible values:

- Warning (fatal, toxic, harmful, may be harmful)
- Danger (fatal, toxic, harmful, may be harmful)
- Not classified
- --- No animal toxicity data available

Criteria used to select the appropriate category

	Category	1	2	3	4	5	Not classified
Acute toxicity (mg/kg)							
	label	Fatal	Fatal	Toxic	Harmful	May be Harmful	
Oral		0-5	5-50	50-300	300-2000	2000-5000	>5000
Skin		0-50	50-200	200-1000	1000-2000	N.A.	>2000
Chronic toxicity (mg/kg/day)							
	Category	1			2		
	label	Known risk of serious damage following repeated or prolonged exposure			May cause severe damage following repeated or prolonged exposure		
Oral	Subacute	0-30			30-300		
	Subchronic	0-10			10-100		
	Chronic	0-3			3-30		
Skin	Subacute	0-60			60-600		
	Subchronic	0-20			20-200		
	Chronic	0-6			6-60		

4- Exposure scenario

- Duration in minutes: Duration can be entered manually in the corresponding textbox (a valid duration is a whole number greater than 0 and less or equal to 480). After entering the duration, it is necessary to press ENTER to update calculation of the hazard index.
- Body parts exposed: Potential exposed skin from 10 different body parts can be selected by checking the checkbox next to the name of the body part exposed. More than one body part can be selected simultaneously to estimate the equivalent dermal exposure risk. Changes are shown automatically as checkboxes are checked or unchecked.
- If there is significant simultaneous inhalation exposure, check the corresponding checkbox provided by clicking on it; if not, leave the checkbox empty.

5- DHR

DHR is the Dermal Hazard Ratio, representing after the exposure scenario has been chosen by user, a ratio between the dose potentially absorbed through dermal contact and a 'reference dose' that would correspond to an 8-hour inhalation exposure at the level of an occupational exposure limit (OEL). The estimation of DHR is accompanied by an incertitude analysis based on Monte Carlo simulation.

In estimating the relevant risk threshold:

1- When simultaneous inhalation exposure is absent, the relevant risk threshold is taken as 100% of the maximal allowed inhalation dose.
2- When simultaneous inhalation exposure is present, the relevant risk threshold is taken as 10% of the maximal allowed inhalation dose.

Displayed results:

- The estimated DHR value in the white box (represented as a blue star on the graph)
- Value in the green box is the probability that the potential cutaneous dose is less than this threshold (corresponds to the green section on the graph)
- Value in the orange box is the probability between 10% inhaled and 100% inhaled threshold (corresponds to the orange section on the graph)
- Value in the red box is the probability that the potential cutaneous dose is greater than this threshold (corresponds to the red section on the graph)
- A message pointing out either the probability that the potential cutaneous dose is greater than a threshold if the estimated DHR exceeds the relevant risk threshold suggested OR the probability that the potential cutaneous dose is less than a threshold if the estimated DHR is below the relevant risk threshold
- Possible warning messages may be displayed:
    - If the reference dose was not derived from an existing OEL value but estimated based on animal toxicity data, a message warns that the

uncertainty factor around the DHR value has been increased to take into account this added uncertainty.

- If the reference dose was calculated from an OEL known to be based on a local effect (e.g. irritation), the following message is displayed : the reference value used to calculate the DHR comes from an OEL not relevant to systemic toxicity and thus the risk is overestimated to an unknown extent.
- If the substance is associated with risk phrases corresponding to skin irritation or if the RTECS database contains positive skin irritation tests for the substance, a message warns the user that skin penetration could be enhanced by direct skin damage.
- A warning message will be displayed if the chemical is volatile, proposing that the calculated DHR might be overestimated if cutaneous contact is intermittent (i.e. there is potential for evaporation of the dose applied to the skin before penetration occurs)
- A warning message will be displayed if the selected agent has been flagged as either possibly carcinogenic or mutagenic by the European community. For such agents it is uncertain whether a practical threshold exists for harmful effect. Minimizing exposure should be a priority notwithstanding the actual DHR value.
- A warning message will be displayed if the selected agent is classified as a sensitizer (Risk Phrase 43): the model used in UPERCUT does not allow assessment of risk of sensitization
- If the selected agent has low toxicity but is irritant and has an OEL, DHR might wrongly reflect risk. A warning message will be displayed stating that there is no evidence of systemic toxicity from animal data, but a DHR was calculated because an OEL exist or was predicted. The DHR might indicate skin penetration but might not reflect an actual health risk.

- Possible error messages may be displayed:
  - If molecular weight and/or LogKow are outside of QSAR (Quantitative structure-activity relationship) model bounds, DHR will consequently not be calculated and an error message will be displayed.
  - If a reference dose could not be calculated (no existing OEL and no animal toxicity data), DHR will not be calculated and an error message will be displayed.

Jérôme Lavoué, Version December 2015