# Supplementary Materials

**Contents**

S1: Chemical structures of Itraconazole (ITZ), hydroxyitraconazole (HITZ), and internal standard R051012

S2: Algorithm of total hazard value of solvents

S3: Algorithm of combinational weighted TOPSIS

S4: Normalized values and ranking orders and of extraction efficiency, greenness, and combinational weighted TOPSIS

# S1: Chemical structures of Itraconazole (ITZ), hydroxyitraconazole (HITZ), and internal standard R051012



# S2 Algorithm of total hazard value of solvents

**Total Hazard Value (HVT)** is calculated as follows:

**HVT = (EH + EE) × FEXP**

where,

EH and EF are effects of solvent on human health and environment, respectively. FEXP is exposure factor of solvent.

EH, EE and FEXP are respectively calculated as follows:

(1) EH = HVOR + HVINH + HVCAR + HVNC

(2) EE = HVMAM + HVFA + HVFC

(3) FEXP = HVBOD + HVHYD + HVPHO +HVBCF + HVVOL.

**(1). Human Health Effects，EH**

EH = HVOR + HVINH + HVCAR + HVNC

HVOR: Hazard value for acute oral toxicity, calculated based on the rodent acute LD50 (mg/kg) data as follows:

HVOR = 0, LD50 > 5,000

HVOR = 6.2 – 1.7lg LD50, 5 < LD50 ≤ 5,000

HVOR = 5, LD50 ≤ 5

HVINH: Hazard value for acute inhalation toxicity, calculated based on the rodent acute LC50 (ppm) data as follows:

HVINH = 0, LC50 > 10,000

HVINH = 8.0 – 2.0lg LC50, 31.6 ≤ LC50 ≤ 10,000

HVINH = 5, LC50 < 31.6

HVCAR: Carcinogenicity. Scores for carcinogenicity, based on International Agency for Research on Cancer (IARC) and Environmental Protection Agency of United States (EPA) classifications.

HVNC: Other specific human health effect, include mutagenic effects, developmental effects, reproductive effects, neurotoxicity, and other chronic effects. Each identified effect scores a value of one.

**(2). Environmental effects, EE**

EE = HVMAM + HVFA + HVFC

HVMAM: Hazard value for territorial effects, assigned and calculated as for human acute oral effects.

HVFA: Hazard value for acute aquatic toxicity, calculated as follows:

HVFA = 0, LC50 ≥ 1,000

HVFA = 5.0 – 1.67lg LC50, 1 ≤ LC50 ≤ 1,000

HVFA = 5, LC50 < 1

HVFC: Hazard value for chronic aquatic toxicity, calculated in 2 steps as follows:

NOEL = 0.25 (LC50), log Kow < 2

NOEL = LC50/(5.3lg Kow – 6.6), 2 ≤ log Kow < 5

NOEL = 0.05 (LC50), log Kow ≥ 5

where, NOEL is no-observable-effect level, and is Kow is water partition coefficient, subsequently,

HVFC = 0, NOEL > 100

HVFC = 3.33 – 1.67lg NOEL, 0.1 < NOEL ≤ 100

HVFC = 5, NOEL ≤ 0.1

**(3). Exposure Factor, FEXP**

FEXP = HVBOD + HVHYD + HVPHO + HVBCF.

HVBOD: Hazard value with respect to the half time (t1/2) of Biological oxygen demand (BOD), calculated as follows:

HVBOD = 1, t1/2 ≤ 4d

HVBOD = 0.311(lnt1/2) + 0.569, 4d < t1/2 ≤ 500d

HVBOD = 2.5, t1/2 > 500d

HVHYD：Hazard value with respect to the half time (t1/2) of hydrolysis,

HVPHO: Hazard value with respect to the half time (t1/2) of photolysis. Both HVHYD and HVPHO are calculated the same as HVBOD.

HVBCF: Hazard value with respect to Bioconcentration Factor (BCF), it is calculated in 2 steps:

log BCF = 0.910 (log Kow) – 1.975 log (6.8 × 10-7 KOW + 1) – 0.786

subsequently, HVBCF = 0.5(log BCF) + 0.5 1.0 < log BCF ≤ 4.0

HVBCF = 1 log BCF ≤ 1.0

HVBCF = 2.5 log BCF > 4.0

HVVOL: hazard value related to exposure via inhalation in laboratory, can be calculated as follows :

HVVOL = 3 - 0.01×BP 50 °C≤ BP ≤ 200 °C

HVVOL = 1 BP ≥ 200 °C

HVVOL = 2.5 BP < 50 °C

where, BP is the boiling point of solvent.

# S3 Algorithm of combinational weighted TOPSIS

Algorithm of the entropy-based TOPSIS mainly consists of the following seven steps:

## Step 1: Establish a decision matrix

Assume a MCDA problem has *m* alternatives and each alternative is evaluated against *n* criteria. To obtain the performance of a set of alternatives on a given set of criteria, a decision matrix A of *m* × *n* dimension is constructed initially. Denote *aij* as the *jth* criterion’s value in the *i*th alternative. Thus, a MCDA problem can be concisely expressed in a matrix format as follows:

A = (*aij*)*m*×*n* = ,

1 ≤ *i* ≤ *m*, 1 ≤ *j* ≤ *n*

## Step 2: Normalize the decision matrix

The normalized decision matrix is denoted as *rij* which is calculated depending on the property of *aij*. If aij represents benefit, *i.e*., it is the bigger the better, then

*rij* = (1)

If *aij* denotes cost, *i.e*., it is the smaller the better, then

*rij* = (2)

The standardized decision matrix is as follows:

*R* = (*rij*)*m*×*n* =

In this paper, enrichment factor (EF) and chromatographic resolution (Rs) denotes benefit and hazard value (HV) denotes cost.

## Step 3: Calculate the objective weight (entropy weight, *ωj1*)

(1) Calculate probability of each evaluation criterion (*pij*) as follows:

*pij* = , where, 0

(2) Calculate entropy value (*ej*) of each evaluation criterion as follows:

*ej* = - , where，0 ≤ *ej* ≤ 1, when *pij* = 0, *pij*ln*pij* = 0.

(3) Calculate disparity of evaluation value (*dj*) of each criterion as follows:

*dj =* 1 *– ej*, where, 0

(4) Calculate weight of each criterion (*ωj1*) as follows:

*j1 =*

For each alternative *ai* with respective evaluation criterion *j*, the smaller the entropy value (*ej*), the larger thedisperity of the evaluation value (*dj*) and entropy weight (*ωj*), *i.e*. the certain alternative contains more valuable information for the investigation criterion.

## Step 4: calculate the subjective weight (*ωj2)*

The subjective weight is determined based on expert evaluation.

## Step 5: Calculate the comprehensive weight

Both the objective and subjective weights are normalized, and the comprehensive weight is calculated as follows:

ω*i* = *α1*ω*i1* + *α2*ω*i2* ,

where, α*1* and α*2* are the weighting factors, in the current study, *α*1 = *α*2 = 0.5

## Step 6: Construct the weighted decision matrix

Denote *uij* = *i* × *rij*, transform the standardized decision matrix *R* = (*rij*)*m×n* into the weighted decision matrix as follows:

*U* = (*uij*)*m×n* =

## Step 7: Determine the positive-ideal and negative-ideal solutions

Denote *U+* and *U-* as positive-ideal and negative-ideal solution of the alternatives, respectively.

= =

= =

where, *j*+ and *j*- represent the sets of benefit criteria and cost criteria, respectively, 1 ≤ *j* ≤ *n*.

## Step 8: Compute the Euclidean distance (Di).

= , (*i* = 1,2,)

= , (*i* = 1,2,)

where, *Di*+ and *Di*- represent the Euclidean distance of each alternative from the positive-ideal and negative-ideal solutions, respectively.

## Step 9: Calculate the relative closeness (Ci) of each alternative and rank the preference order.

The relative closeness *Ci* is computed as follows,

*Ci* = , (*i* = 1,2, (3)

*Ci* demonstrates how close the alternative is to the ideal solution and how far the alternative is from the negative-ideal solution. The *Ci* value ranges from 0 to 1. The closer *Ci* values to 1 is, the closer the alternative is to the ideal solution, whereas the closer *Ci* values to 0, the closer the alternative is to the negative solution.

# S4 Normalized values and ranking orders and of extraction efficiency, greenness, and combinational weighted TOPSIS

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| No. | Extraction Efficiency | |  | Chromatographic Resolution | |  | Greenness | |  | *Ci*a-combinational weight | |
| Normalized Value | Rank |  | Normalized Value | Rank |  | Normalized Value | Rank |  | Normalized Value | Rank |
| 1 | 0.0774 | 6 |  | 0.4333 | 4 |  | 0.3683 | 6 |  | 0 | 8 |
| 2 | 0.9135 | 2 |  | 0 | 8 |  | 0.0230 | 7 |  | 0.6085 | 3 |
| 3 | 1 | 1 |  | 0.1000 | 7 |  | 0 | 8 |  | 0.6580 | 2 |
| 4 | 0 | 8 |  | 0.3667 | 5 |  | 0.6133 | 4 |  | 0.1353 | 7 |
| 5 | 0.1065 | 4 |  | 1 | 1 |  | 0.7665 | 3 |  | 0.2914 | 4 |
| 6 | 0.7146 | 3 |  | 0.7667 | 2 |  | 1 | 1 |  | 1 | 1 |
| 7 | 0.0982 | 5 |  | 0.3333 | 6 |  | 0.5708 | 5 |  | 0.1491 | 6 |
| 8 | 0.0666 | 7 |  | 0.6333 | 3 |  | 0.7983 | 2 |  | 0.2800 | 5 |

a: *Ci* - Relative closeness coefficient which demonstrates the result of TOPSIS method. The set of solvent pairs is ranked according to the descending order of the *Ci*