

Multi-agent artificial intelligence enables rapid medical device biocompatibility assessment

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ILLUSTRATIVE CASE • ISO 10993-17:2023

An audit-ready TRA in under 15 minutes

THREE EXTRACTABLES • ONE PROMPT

AIM

Determine whether an agentic system can execute a complete quantitative toxicological risk assessment — point-of-departure selection, uncertainty-factor derivation, exposure modelling and margin computation — from an extractables table alone, and whether its judgement calls survive expert review.

STATED ASSUMPTION SET

Contact duration category	≥ 366 d – all four windows
Body weight, adult default	BW 60 kg
Device-count scaling factor	SF = 1
Release data	Assumed release, Rd
Use pattern	Single-use, non-repeat

The use scenario was not supplied. Conservative defaults were substituted, labelled as defaults, and every downstream value is conditional on them.

AUDIT TRAIL

Tolerable-intake derivations	6
Exposure-dose calculations	3 × 4 windows
In silico screens, dual-model	3 constituents
Independent recomputation	Yes
Primary records cited	25

Every tool call is logged, negative results included. Report generation ran in under 15 minutes.

FIG. 1 – TOLERABLE INTAKE AND CANCER-RISK-SPECIFIC DOSE, WITH THE FULL UNCERTAINTY-FACTOR CHAIN

CONSTITUENT – ENDPOINT	POD µg/kg/d	POD type	UNCERTAINTY FACTORS					MF	TI / CRSD µg/kg/d
			Intra	Inter	Route	Duration	Pod-type		
BHT – reproductive, chronic	25,000	NOAEL	10	10	2	1	1	200	125
Irganox 1076 – subacute	30,000	NOAEL	10	10	10	1	1	1,000	30
Irganox 1076 – subchronic	34,000	NOAEL	10	10	10	1	1	1,000	34
Irganox 1076 – chronic	64,000	NOAEL	10	10	10	1	1	1,000	64
Irganox 1076 – developmental (sensitivity)	32,090	LOAEL	10	10	10	1	10	10,000	3.21
MDA – non-cancer, chronic	7,100	NOAEL	10	10	2	6	1	1,200	5.92
MDA – cancer, slope factor	n/a	Formula C.3	–	–	–	–	–	none	0.00625

ROUTE UF 2 for BHT and MDA, both with documented ~90% oral bioavailability; 10 for Irganox 1076, for which no bioavailability data exist. The 5-fold difference in stringency follows from data availability, not from a judgement call, and it is why the Irganox margins are thin.

FIG. 2 – MARGIN OF SAFETY, PER ENDPOINT AND EXPOSURE WINDOW

ENDPOINT	≤ 1 d	2–30 d	31–365 d	≥ 366 d
BHT	93.8	187.5	2,906	34,312
Irganox 1076	1.5	3.0	52.7	1,171
MDA – non-cancer	23.7	47.3	734	8,662
MDA – cancer, per period	0.025	0.050	0.775	9.15

Thirteen of sixteen margins exceed unity. The three that do not are the per-period cancer comparison, where an Annex E peak-window exposure estimate is set against a potency factor calibrated to lifetime-average daily dose. On the lifetime-average metric the excess risk is 1.57×10⁻⁸, or 639× below the 1×10⁻⁵ criterion — corroborated independently against the OEHHA no-significant-risk level.

BHT tolerable intake vs EFSA ADI	MDA non-cancer vs ATSDR MRL
Half, explained by the route factor	13× below intermediate-duration

THE REQUESTER’S PROMPT, IN FULL

“Three chemicals from a blood-contacting device: BHT 80 µg, Irganox 1076 1,200 µg, MDA 15 µg. Please run a full ISO 10993 tox risk assessment.”

FIG. 3 – THE DELIVERED REPORT

- 01 Fifteen sections: hazard identification, derivation, exposure, margins, sensitivity, limitations, recommendations.
- 02 A verdict per constituent, with the fragile pass and the formal trigger both stated rather than smoothed over.
- 03 Every substituted default labelled as a default, with its sensitivity if wrong.
- 04 Cross-checks against EFSA, ATSDR and OEHHA values, reported beside the derivation they test.
- 05 A complete tool log, negative findings included, so the search strategy itself can be audited.

<15MIN RUNTIME

16MARGINS DERIVED

25PRIMARY RECORDS

CONCLUSIONS

- 01 All three constituents were tolerable under the stated assumptions; residual uncertainty was quantified rather than asserted.
- 02 The judgement calls — screening override, POD mapping, dose-metric check, fragility test — matched expert practice and are on record with their reasoning.
- 03 Every uncertainty factor, source and computation is recorded, so each margin can be re-derived independently.
- 04 Toxicologist review remains required before submission.

REFERENCES

1. ISO 10993-17:2023 *Biological evaluation of medical devices — Part 17*. · 2. ISO 10993-1:2018. · 3. EFSA ANS Panel. Re-evaluation of butylated hydroxytoluene (E 321). *EFSA J.* 2012;10(3):2588. · 4. ECHA. Registered substance factsheets and harmonised classification, EC 202-974-4. · 5. OEHHA. No Significant Risk Level for 4,4'-methylenedianiline.

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