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Important aspects and approaches in carrying out a toxicological risk assessment on E&L for medical devices with focus on requirements of the MDR

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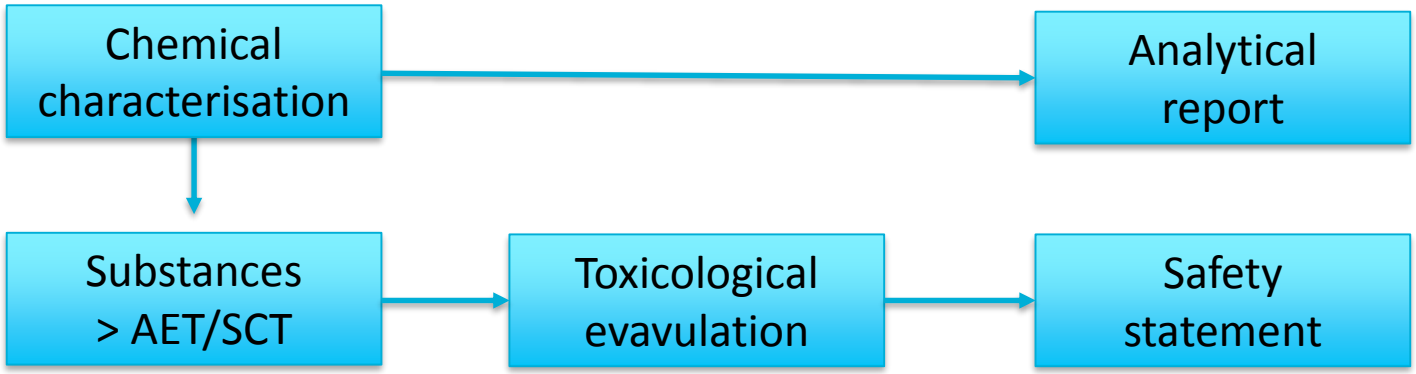
A. Introduction: ISO 10993-18/17/1

- Chemical characterization (ISO 10993-18) coupled with toxicological risk assessment.
  - Estimate the actual case chemical release; perform an extraction study whose design (exhaustive, exaggerated, simulated) is consistent with the clinical conditions of use.
  - Identify, quantify and report all Extractables & Leachables (E&L) > AET (SCT).
- Biological evaluation: establish allowable limits (ISO 10993-17)
- Biological evaluation & testing (ISO 10993-1)



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A. Introduction: ISO 10993-18/17/1

- Toxicological evaluation of E&L
  - **Exposure assessment**
    - Type of exposure (surface, externally communicating, implant)?
    - Duration (limited, prolonged, permanent)?
    - Type of patient (age, sex, body mass)?
  - **Hazard assessment: threshold or non-threshold?**
    - Relevant toxicity endpoints (see further) …
    - Starting descriptors: NOAEL, LOAEL, TD_{50} …
    - Safety limits TI, TE, TCL, RfD, ADI, MRL, ….
  - **Risk characterization**
    - **Safety margin: Safety limit / Max. exposure**

Maximum exposure (mg/day)?

Most conservative **safety limit** (mg/day)?

> 1: OK **< 1 : further testing**

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B. major toxicological endpoints & thresholds

(1) Genotoxicity & carcinogenicity

(2) Sensitization & allergic potential

(3) Local tolerance (irritation)

(4) General systemic toxicity

(5) Reproductive & developmental toxicity

…

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B. Major toxicological endpoints & thresholds

(1) Genotoxicity & carcinogenicity

- **Genotoxicity:** based on short term assays
  1. Bacterial mutation (*in vitro:* Ames test)
  2. Mammalian gene mutation (*in vitro:* Mouse Lymphoma)
  3. Chromosomal aberration (structural/numerical)
  4. …

  In vitro → *in vivo*

- **Carcinogenicity:** based on long term assays
  1. 24-month carcinogenicity study in rats/mice
  2. Or: 6-month transgenic assays in mice
  3. Or: Initiation-promotion test models
  4. Or: …

  in vivo

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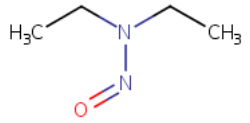
(1) Genotoxicity & carcinogenicity

- **Genotoxicity**

E.g. diethylnitrosamine



1. Interaction with DNA
   - ➢ Mutations (bacterial/mammalian cells).
2. Interaction with cell division
   - ➢ Chromosome aberrations / Micronucleus formation.

- **Carcinogenicity**

1. Genotoxic carcinogenicity:

   1/100.000 – 1/1.000.000 risk is acceptable. … or **threshold**?

   - ➢ fast, invasive, malignant.
2. Non-genotoxic carcinogenicity
   - ➢ slow, encapsulated, benign.

B. Major toxicological endpoints & thresholds

(2) Sensitization & allergic potential

- **Preclinical data:** based on short term assays
  1. Local Lymph Node Assay (LLNA) in mice
  2. Guinea-pig maximization test (GMPT) or Buehler test
  3. New *in vitro* models (for chemicals)
  4. …
- **Clinical data:** based on short term assays or case studies
  1. Human Repeat Insult Patch Testing (HRIPT)
  2. Case studies of allergic contact dermatitis (ACD)
  3. Case studies of anaphylactic reactions/shock
  4. …

In vivo

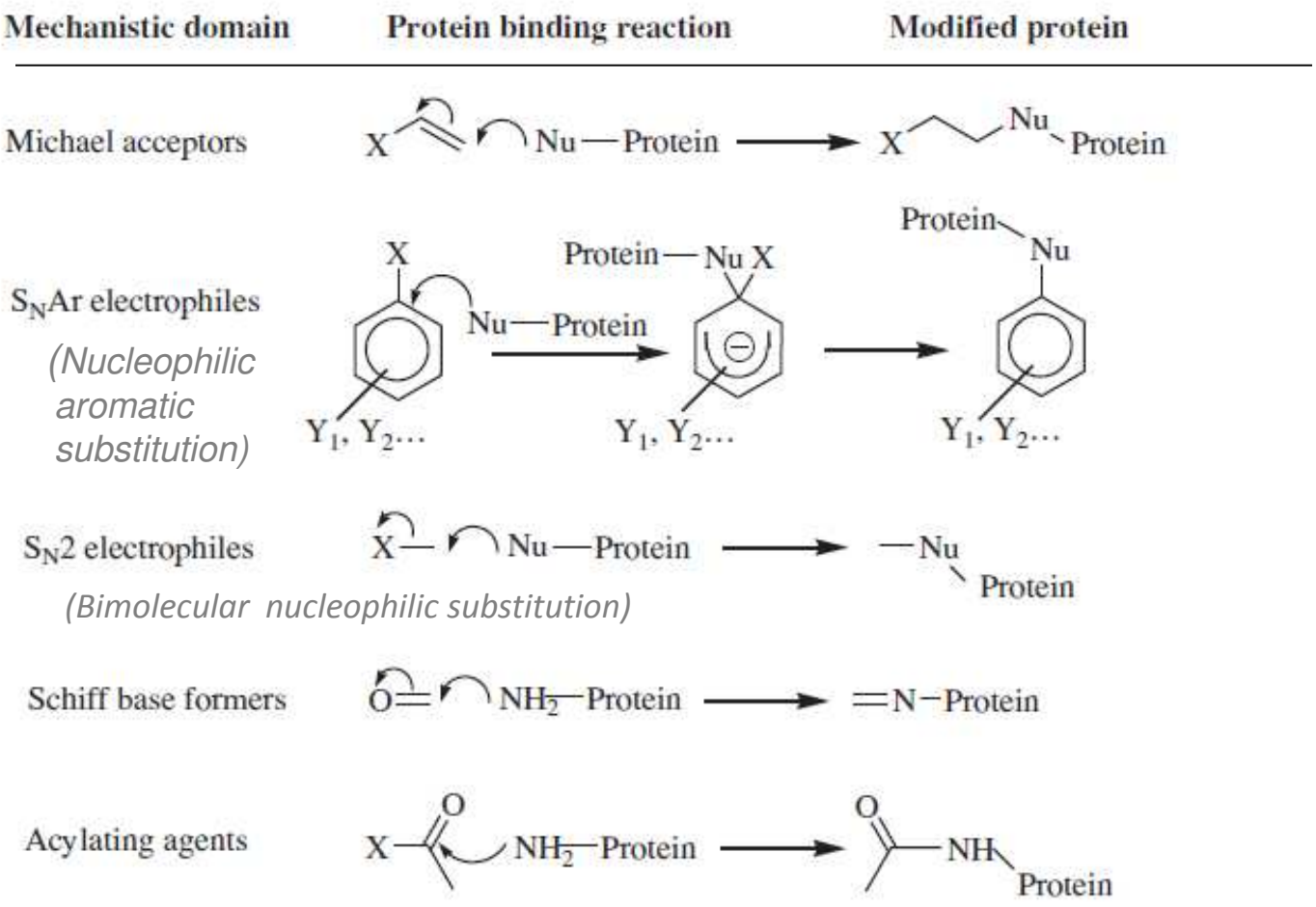
No / Weak / Moderate / Severe / Extreme sensitizer

(2) Sensitization & allergic potential

- Induction phase
  - First contact with allergen
    - ➢ Protein binding (hapten formation)
      - ➢ Activation of Macrophages / T-Lymphocytes
        - ➢ No symptoms
- Elicitation phase
  - Second/later contacts with allergen
    - ➢ T-Lymphocyte activation (immunological memory)
      - ➢ Infllammatory response
        - ➢ Symptoms (swelling, redness)

(2) Sensitization & allergic potential

Protein binding groups



B. Major toxicological endpoints & thresholds

(3) Local tolerance (irritation)

- **Preclinical data:** based on short term assays
  1. *In vivo* local tolerance testing in rabbits
  2. *In vivo* skin/eye acute irritation assays in rabbits
  3. *In vitro* skin irritation assays
     - Transcutaneous Electrical Resistance (TER)
     - Human skin model
  4. …
- **Clinical data:** based on short term assays/case studies
  1. Human Skin irritation test
  2. Case studies of skin/mucosa irritation
  3. …

In vitro → *in vivo*

No Irritation concentration limits?

(4) General systemic toxicity

Based on data from

- **Single dose toxicity (acute)**
  - LD_{50} = Lethal dose in 50% of animals
  - Maximum tolerated dose (MTD)
  - Target organs

In vivo

LD_{50}?

- **Repeated dose toxicity (subacute, subchronic, chronic)**

  Subacute 28-day Toxicity Study in Rodents

  Subchronic 90-Day Toxicity Study in Rodents

  Subchronic 90-Day Toxicity Study in Non-rodents

  Chronic 6-9 month Toxicity Study in Rodents /Non-Rodents

  - Target organs?

In vivo

NO(A)EL?
LO(A)EL?

(4) General systemic toxicity

If no data: Cramer classes* (Munro et al, 1996) → Non-cancer TTC

1. **Class I: low order of toxicity**
   Substances of simple chemical structure with known metabolic pathways and innocuous end-products which suggest a low order of oral toxicity.
   -> NOAEL (5%ile): 3 mg/kg/day -> **Non-cancer TTC = 1800 µg/day**
2. **Class II: intermediate toxicity**
   Substances less innocuous than substances in class I, but do not contain structural features suggestive of toxicity like those substances in class III. May contain reactive functional groups.
   -> NOAEL (5%ile): 0,91 mg/kg/day -> **Non-cancer TTC oral = 540 µg/day**
3. **Class III: possible significant toxicity**
   Substances of a chemical structure that permit no strong initial presumption of safety, or may even suggest significant toxicity.
   -> NOAEL (5%ile): 0,15 mg/kg bw/day -> **Non-cancer TTC = 90 µg/day**

*** Database of >600 substances**

-> Food additives, pharmaceuticals, chemicals, plant protection agents, cosmetics

(5) Reproductive & Developmental toxicity

Based on data from

- **Reproductive toxicity studies, e.g.**

  Screening fertility study in male/female rats
  One-generation reproductive toxicity study in rats
  Two-generation reproductive toxicity study in rats
  Extended one-generation reproductive toxicity study in rats

  ➢ Fertility effects? Secondary to parental toxicity?

  In vivo

  NO(A)EL?
  LO(A)EL?

- **Developmental toxicity studies, e.g.**

  Developmental toxicity in rats/mice
  Developmental toxicity in rabbits/ … (other non-rodent)
  Two-generation reproductive toxicity study in rats
  (Extended) One-generation reproductive toxicity study in rats

  ➢ Teratogenicity? Embryotoxicity/Foetotoxicity?

  ➢ Secondary to maternal toxicity?

  In vivo

  NO(A)EL?
  LO(A)EL?

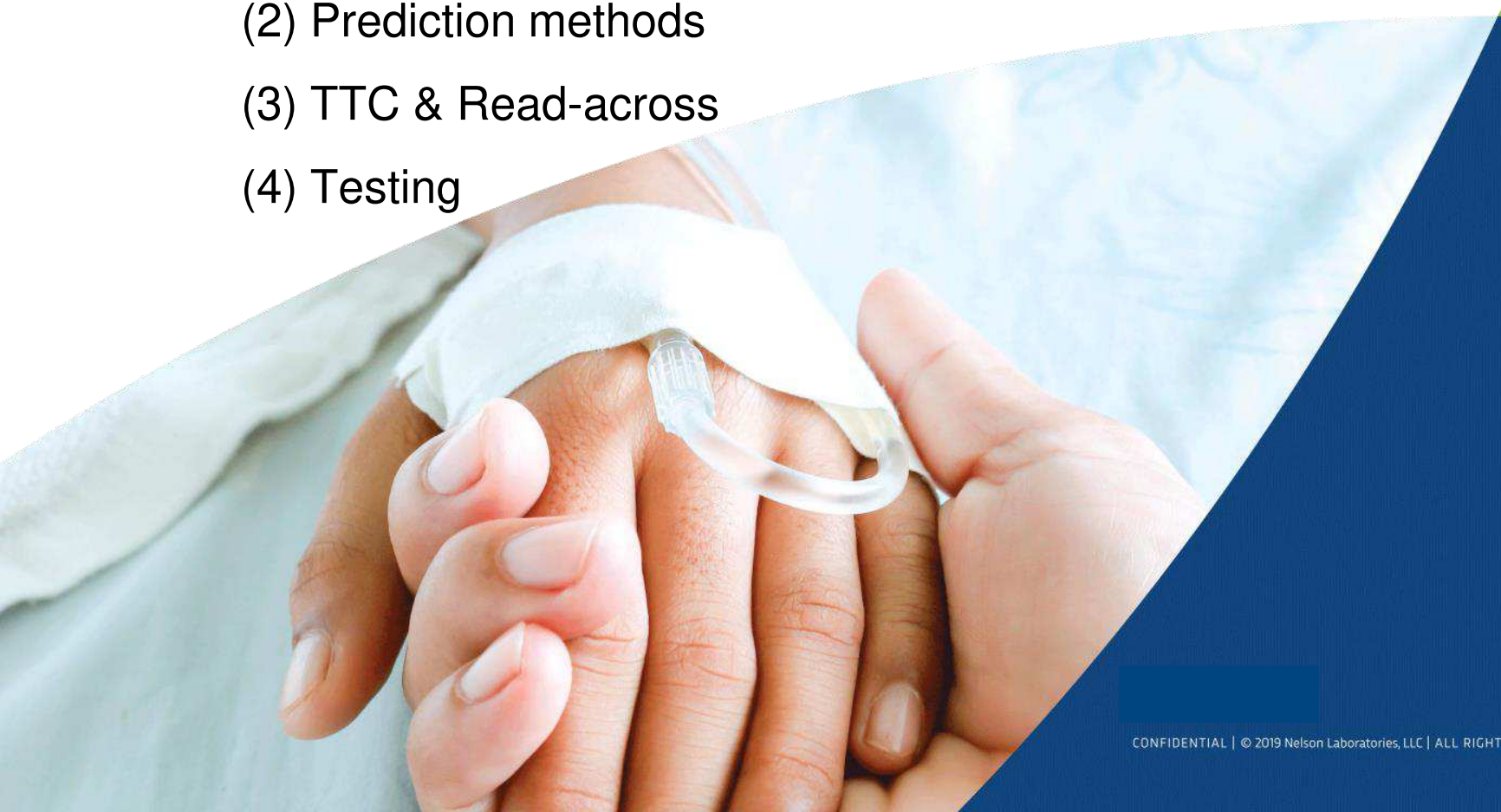
C. HAZARD EVALUATION METHODS

(1) Literature search

(2) Prediction methods

(3) TTC & Read-across

(4) Testing



(1) Literature search

- **Databases**
  - **Free online sources**

Toxnet:
- CCRIS
- CPDB
- Gene-Tox
- HSDB
- IRIS

…

ECHA Registered substances

eCHEMPORTAL

National Toxicology Program …

  - **Commercial databases**

RTECS
ELSIE
COSMOS
ToxPlanet …

C. Hazard evaluation methods

(1) Literature search

- http://www.toxicology.org/groups/ss/MDCPSS/resources.asp

(2) Prediction methods

Rule based

- **(Q)SAR systems:**
  - **DEREK = Deductive Estimation of Risk from Existing Knowlegde**
    - **Enpoints selected:** bacterial mutagenicity (5 strains), genotoxicity, carcinogenicity, sensitization, irritation, systemic toxicity, …
    - **Reporting:**
      - **Alerts found:** e.g. : 352 Aromatic amine or amide
      - **Reasoning:** e.g. Mutagenicity is PLAUSIBLE / PROBABLE …

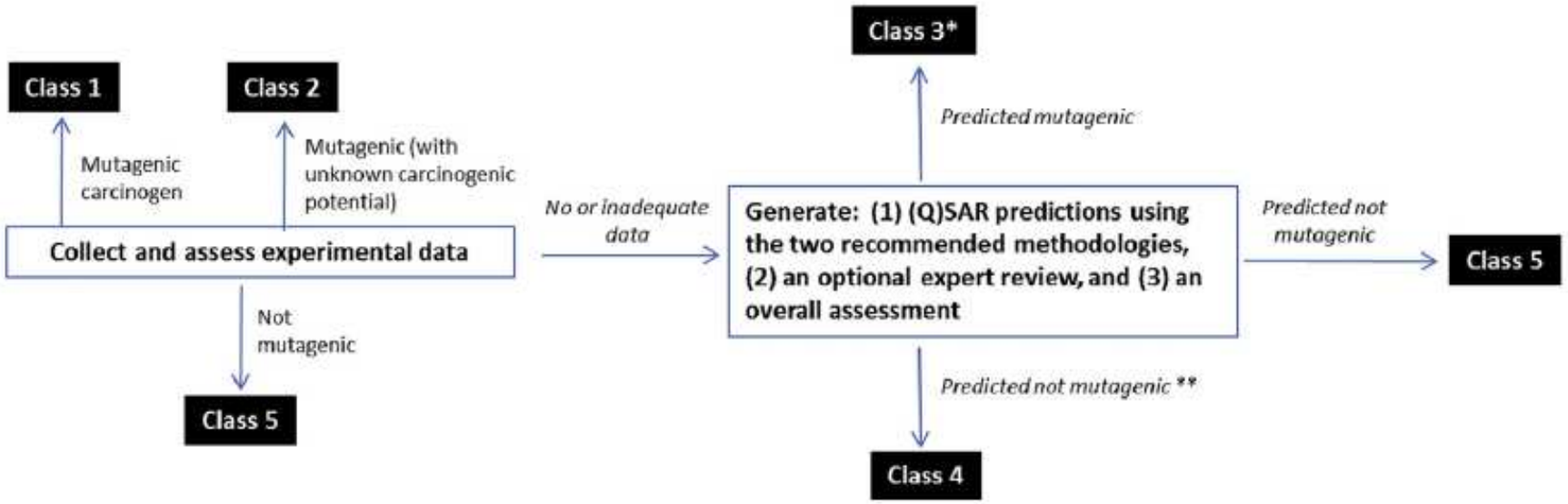
Statistically based

  - **Multicase (CASE Ultra) → *"toxicophores"***
    - **Enpoint selected:** mutagenicity (5 strains), genotoxicity, carcinogenicity, senzitisation, …
    - **Reporting:**
      - **Alerts found:** NEGATIVE or POSITIVE / DEACTIVATING
        e.g.: Alert ID 49: cH:c (-C3H2):c
      - **Probability :** < 40 (negative); 40-60 (inconclusive); >60 (positive)
  - **Leadscope, Sarah …**

(2) Prediction methods

Integrated with ICH M7

A. Amberg et al. / Regulatory Toxicology and Pharmacology 77 (2016) 13–24



* Or perform an Ames test

** Based on a shared alert with a known negative

C. Hazard evaluation methods

(3) TTC and Read-across

- TTC mutagenicity/carcinogenicity (ICH M7)
- TTC general toxicity (Cramer rules + Revisions)
- TTC sensitisation (e.g. Dermal sensitisation threshold)
- Read-across with similar compounds …

(4) Testing

- Ames test (Bacterial reverse mutation study)
- Local Lymph Node Assay (LLNA)
- Acute toxicity study (rat)
- Repeated dose toxicity study (14 -28 day)
- Local tolerance testing
- …

D. LIMITS ACCORDING TO ISO 10993-17

(1) Tolerable Intake (TI)

(2)Tolerable Exposure (TE)

(3) Tolerable Contact Levels (TCL)

D. Limits According to ISO 10993-17

(1) Tolerable Intake (TI) – *for non-cancer endpoints*

$$TI = \frac{\text{NOAEL, LOAEL, etc.}}{MF\ (UF_1 \cdot UF_2 \cdot UF_3)}$$

- MF: Modifying Factor
- UF_1 (1-10): inter-individual variation among humans (10 = default)
- UF_2 (1-10): extrapolation from data derived in a species other than humans (10 in the absence of data)
- UF_3 (1-100): quality and relevance of the experimental data (1 for good quality and relevant data).

Increase the factor in case of uncertainties:

a) short-term studies being used for extrapolation to longer-term exposures or effects;
b) having only LOAEL data instead of NOAEL data;
c) absence of supporting studies
d) use of animal models inappropriate for the endpoint being assessed;
e) inappropriate route of exposure;
f) rate of exposure;
g) confidence in the database.

(2) Tolerable Intake (TE)

$$TE\ (mg/day) = TI \cdot m_B \cdot UTF$$

- m_B = body mass (kg)
- UTF = CEF · PEF
  a) UTF: Utilization factor
  b) CEF: Concomitant exposure factor (0,2 if the utilization factor is unknown).
  Increase CEF if more than five devices used in any single medical procedure can release the leachable substance.
  c) PEF: Proportional exposure factor (1 is default)
  Decrease PEF to the proportion of the exposure category during which actual exposure to the device is anticipated.

Safety margin

$$= \frac{\textbf{TE … (mg/day)}}{\textbf{Measured E/L (mg/day}}$$

>1: OK

<1: not OK

D. Limits According to ISO 10993-17

(3) Tolerable Contact Level (TCL)

$$TCL\ (mg/cm^2) = \frac{NIL\ or\ MIL}{MF(UF4 \cdot UF5 \cdot UF6) \cdot A}$$

When irritation from direct contact with body tissues is expected.

- MF: Modifying Factor
- MIL: Minimally Irritating Level
  NIL: No Irritating Level
- UF_4 (1-10): inter-individual variation among humans (3-10 = default)
- UF_5 (1-10): extrapolation from data derived in a species other than humans (3 in the absence of data)
- UF_6 (1-30): quality and relevance of the experimental data (1 for good quality and relevant data; 3 for a poorly designed or executed study; 9 if both the relevance and quality of the data are poor). Increase the factor in case of uncertainties
- *A*: body contact surface area (cm^2)

- E. focus on requirements of the MDR

ANNEX I GENERAL SAFETY AND PERFORMANCE REQUIREMENTS - Chapter I. General requirements

10. Chemical, physical and biological properties

(1) Device toxicity and biological safety

(2) Substances of particular concern >0,1%

(2) Risks related to particle size

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(1) Device toxicity and biological safety

10. 1 During devices design/manufacture, particular attention shall be paid to:

(a) the choice of materials and substances used, particularly as regards toxicity and, where relevant, flammability;

(b) the compatibility between the materials and substances used and biological tissues, cells and body fluids, taking account of the intended purpose of the device and, where relevant, absorption, distribution, metabolism and excretion (ADME);

(c) …

- *59. Rules under the old regime applied to **invasive devices do not sufficiently take account of the level of invasiveness and potential toxicity of certain devices** which are introduced into the human body. In order to obtain a **suitable risk-based classification of devices that are composed of substances or of combinations of substances that are absorbed by or locally dispersed in the human body,** it is necessary to introduce specific classification rules for such devices. The classification rules should take into account the place where the device performs its action in or on the human body, where it is introduced or applied, and whether a **systemic absorption of the substances of which the device is composed, or of the products of metabolism in the human body** of those substances occurs.*

(2) Substances of particular concern >0,1%

10. 4.1 Devices, or those parts thereof or those materials:

- that are **invasive and come into direct contact with the human body**,
- **(re)administer medicines, body liquids or other substances**, including gases, to/from the body, or
- **transport or store such medicines, body fluids or substances**, including gases, to be (re)administered to the body,

shall only contain the following substances in a concentration that is above 0,1 % w/w where justified pursuant to Section 10.4.2:

a) substances which are carcinogenic, mutagenic or toxic to reproduction ('CMR'), of category 1A or 1B, in accordance with Part 3 of Annex VI to CLP Regulation (EC) No 1272/2008.

b) substances having endocrine-disrupting properties for which there is scientific evidence of probable serious effects to human health and which are identified either in accordance with the procedure set out in Article 59 of REACH Regulation (EC) No 1907/2006 of the European Parliament and of the Council (2) or, once a delegated act has been adopted by the Commission pursuant to the first subparagraph of Article 5(3) of Regulation (EU) No 528/2012 of the European Parliament and the Council (3), in accordance with the criteria that are relevant to human health amongst the criteria established therein.

(2) Substances of particular concern >0,1%

10. 4.2 Justification regarding the presence of CMR and/or endocrine-disrupting substances shall be based upon:

(a) an analysis and estimation of potential patient or user exposure to the substance;

(b) an analysis of possible alternative substances, materials or designs, including, where available, information about independent research, peer-reviewed studies, scientific opinions from relevant scientific committees and an analysis of the availability of such alternatives;

(c) argumentation as to why possible substance and/ or material substitutes, if available, or design changes, if feasible, are inappropriate in relation to maintaining the functionality, performance and the benefit-risk ratios of the product; including taking into account if the intended use of such devices includes treatment of children or treatment of pregnant or breastfeeding women or treatment of other patient groups considered particularly vulnerable to such substances and/or materials; and

(d) where applicable and available, the latest relevant scientific committee guidelines in accordance with Sections 10.4.3. and 10.4.4.

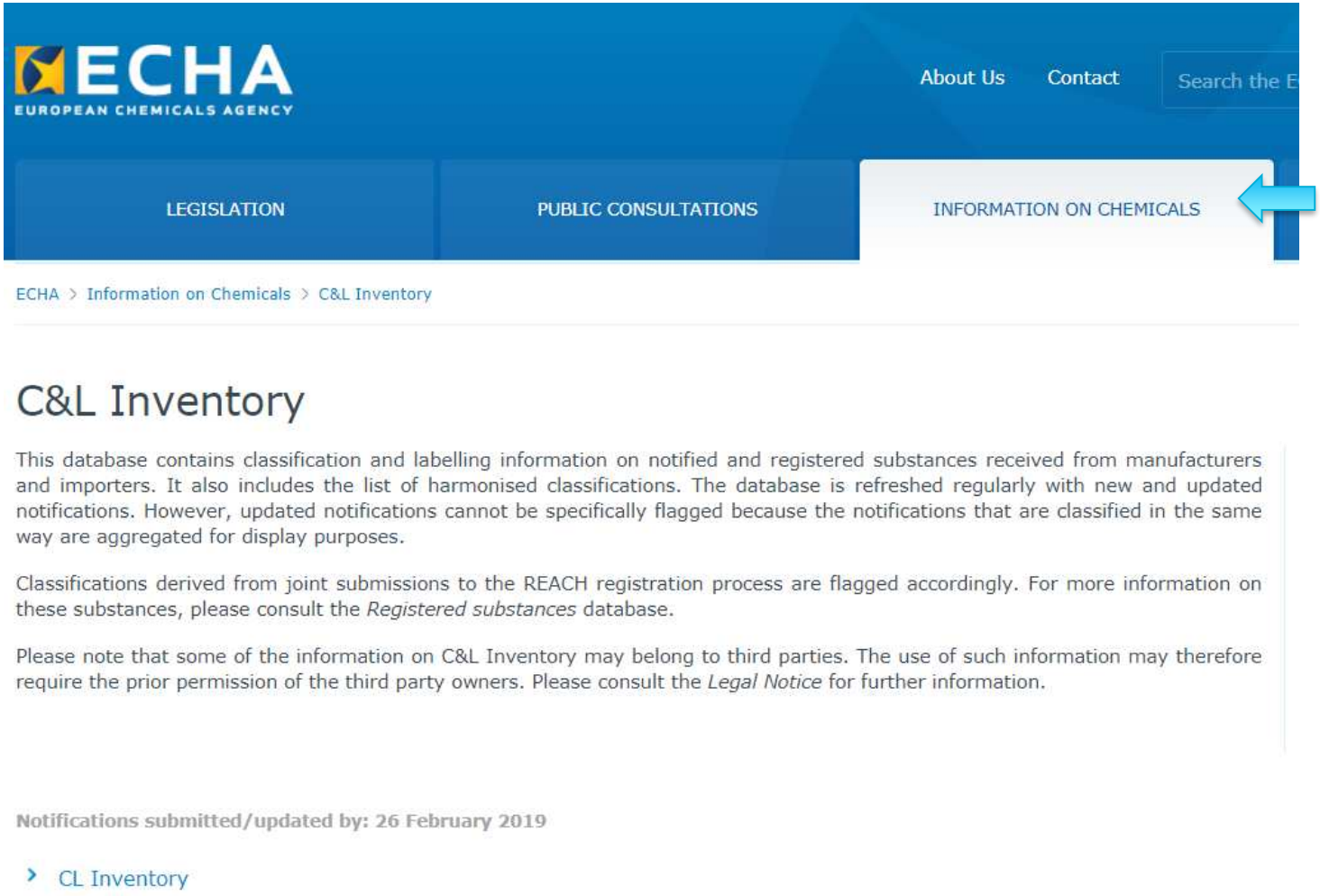
(2) Substances of particular concern >0,1%

10. 4.5 Labelling (CMR & endocrine disrupting substances)

Where devices, parts thereof or materials used therein as referred to in Section 10.4.1. contain substances referred to in points (a) or (b) of Section 10.4.1. in a concentration above 0,1 % weight by weight (w/w), the presence of those substances shall be labelled on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging, with the list of such substances. If the intended use of such devices includes treatment of children or treatment of pregnant or breastfeeding women or treatment of other patient groups considered particularly vulnerable to such substances and/or materials, information on residual risks for those patient groups and, if applicable, on appropriate precautionary measures shall be given in the instructions for use.

E. Focus on the requirements of the MDR

How to find CMR & Endocrine classification? https://echa.europa.e



Example: dihexyl phthalate (CAS 84-75-3; EC 201/559-5)

Summary of Classification and Labelling

Harmonised classification - Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation)

General Information

Index Number	EC / List no.	CAS Number	International Chemical Identification
607-702-00-1	201-559-5	84-75-3	dihexyl phthalate

ATP Inserted / Updated: ATP05

CLP Classification (Table 3)

Classification		Labelling			Specific Concentration limits, M-Factors, Acute Toxicity Estimates (ATE)	Notes
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Supplementary Hazard Statement Code(s)	Pictograms, Signal Word Code(s)		
Repr. 1B	H360FD	H360FD		GHS08 Dgr		

Signal Words	Pictograms
Danger	 Health hazard

(3) Riks related to Particle size

10. 6 Devices shall be designed and manufactured in such a way as to reduce as far as possible the risks linked to the size and the properties of particles which are or can be released into the patient's or user's body, unless they come into contact with intact skin only. Special attention shall be given to nanomaterials.

- *15. There is **scientific uncertainty about the risks and benefits of nanomaterials** used for devices. In order to ensure a high level of health protection, free movement of goods and legal certainty for manufacturers, it is necessary to introduce a uniform definition for nanomaterials based on Commission Recommendation 2011/696/EU (4), with the necessary flexibility to adapt that definition to scientific and technical progress and subsequent regulatory development at Union and international level. **In the design and manufacture of devices, manufacturers should take special care when using nanoparticles for which there is a high or medium potential for internal exposure.** Such devices should be subject to the most stringent conformity assessment procedures. In preparation of implementing acts regulating the practical and uniform application of the corresponding requirements laid down in this Regulation, the relevant scientific opinions of the relevant scientific committees should be taken into account.*

F. Glossary & References

GLOSSARY

- ACD: Allergic Contact Dermatitis
- A(D)I: Acceptable (Daily) Intake
- ADME: Absorption, Distribution, Metabolism, Elimination
- AEL: Acceptable Exposure Level
- AET: Analytical Evaluation Threshold
- CCRIS: Chemical Carcinogenesis Research Information System
- CEF: Concomitant exposure factor
- CLP: Classification & Labelling Package
- CPDB: Carcinogenic Potency Data Base
- EC: European Commission
- E&L: Extractables & Leachables
- ECHA: European Chemicals Agency
- ELSIE: Extractables and Leachables Safety Information Exchange

F. Glossary & References

GLOSSARY

- GENE-TOX: Genetic Toxicology Data Bank
- HRIPT: Human Repeat Insult Patch Testing
- HSDB: Hazardous Substances Data Bank HSDB: Hazardous Substances Data Bank
- IRIS: Integrated Risk Information System
- LD_{50}: Lethal dose in 50% of animals
- LLNA: Local Lymph Node Assay
- LO(A)EL: Lowest Observed (Adverse) Effect Level
- MF: Modifying Factor
- MIL: Minimally Irritating Level
- MoA: Mechanism of Action
- MRL: Maximum Residu Level
- MTD: Maximum Tolerated Dose
- NIL: No Irritating Level

GLOSSARY (CONTINUED)

- NO(A)EL: No Observed (Adverse) Effect Level
- NO(A)EL: No Observed (Adverse) Effect Level
- OECD: Organisation for Economic Cooperation & Development
- PEF: Proportional exposure factor
- REACH: Registration, Evaluation, Restriction & Authorisation of Chemicals
- RfD: Reference Dose
- RTECS: Registry of Toxic Effects of Chemical Substances
- SCT: Safety Concern Threshold
- TD50: Tumorigenic Dose in 50% of the animals
- TTC: Threshold of Toxicological Concern
- UF: Uncertainty Factor
- UTF: Utilization Factor
- WoE: Weight of Evidence

F. Glossary & References

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Thanks for your attention!

QUESTIONS?