

Comments to the Chemical Assessment
Advisory Committee for the IRIS Evaluation of
Ethylene Oxide:
Charge Question #3
Lymphoid cancer-model selection

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Speaking as an independent consultant on behalf of
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ACC modification to Charge

Question 3

- The preferred approach to selecting relevant mode of action (MOA) is to employ current understanding of the molecular mechanisms involved in the pathogenesis of specific lymphoid cancers of interest as the basis for selection.

Does the current hazard assessment, which assumes a mutagenic MOA for ethylene oxide in developing a preferred model for deriving risk estimates for lymphoid cancers, adequately address science that supports different MOAs that are independent of mutagenesis for specific lymphoid cancers?

The implicit assumption that lymphohematopoietic (LHP) cancers (myeloid and lymphoid) all have a common cell of origin or mode of action (MOA) is not scientifically appropriate.

Lymphoid neoplasms specifically represent over 20 distinct diseases with individual MOA's that can be distinguished on the basis of cell of origin, genetics, mechanism of transformation, pathogenesis, etiology and response to therapy.

The cells of origin for >90% of lymphoid neoplasms arise in specific antigen (Ag)- driven mature B- lymphocytes.

Subtype	Frequency	Target cell	Mechanism	Risk Factors
DLBCL/FL	65%	Mature B cell responding to Ag ¹	Specific Ag-dependent	Inflammation Immunosuppression Epstein-Barr Virus
CLL/SLL	10-15%	Small activated B cell ²	Autoimmune restricted Ag-response	Unknown/ Ionizing radiation??
PM (MM)	10-15%	Ag-driven terminal B cell ³	Chronic Ag-stimulation obligatory	Multifactorial-complex Chronic inflammation/ antigenic stimulation/ environment

¹Germinal center follicle in peripheral lymphoid tissue

²Post-germinal center/Memory B cell in peripheral lymphoid tissue

³Terminally differentiated B- cells that have undergone somatic mutation in lymphoid tissue

The remaining cells of origin for <10% of lymphoid neoplasms include mature T lymphocytes or NK cells, and immature progenitor B and T cells.

- Known risk factors include:

- Genetic

- Clonal human viruses (e.g. EBV, HTLV-1, HHV8)

- Immunosuppression

Summary

The consensus in evidence-based medicine does NOT support grouping all LHP cancers or all lymphoid cancers in a single category, because these classifications contain many diverse cancers that are not related with respect to cells of origin, mechanisms or etiology.

- **WHO (2001) Classification of tumours of haematopoietic and lymphoid tissues, IARC Geneva (Jaffe et al, ed).**
- **Morton et al (2006) Lymphoma incidence patterns by WHO subtype in the US 1922-2001. Blood 107: 265-276.**
- **WHO (2008) Classification of tumours of haematopoietic and Lymphoid tissues, IARC Lyon (Swerdlow et al, ed).**
- **Natl. Acad. Sci. (2011) Review of EPA draft IRIS assessment of formaldehyde.**

Recommendation

The preferred approach to selecting a relevant mode of action (MOA) is to employ current scientific evidence-based understanding of the molecular mechanisms involved in the pathogenesis of specific hematopoietic or lymphoid cancers of interest.

Therefore, it is recommended that EPA evaluate each hematopoietic and lymphoid cancer separately, rather than combining them.

Additional clarifying slides

