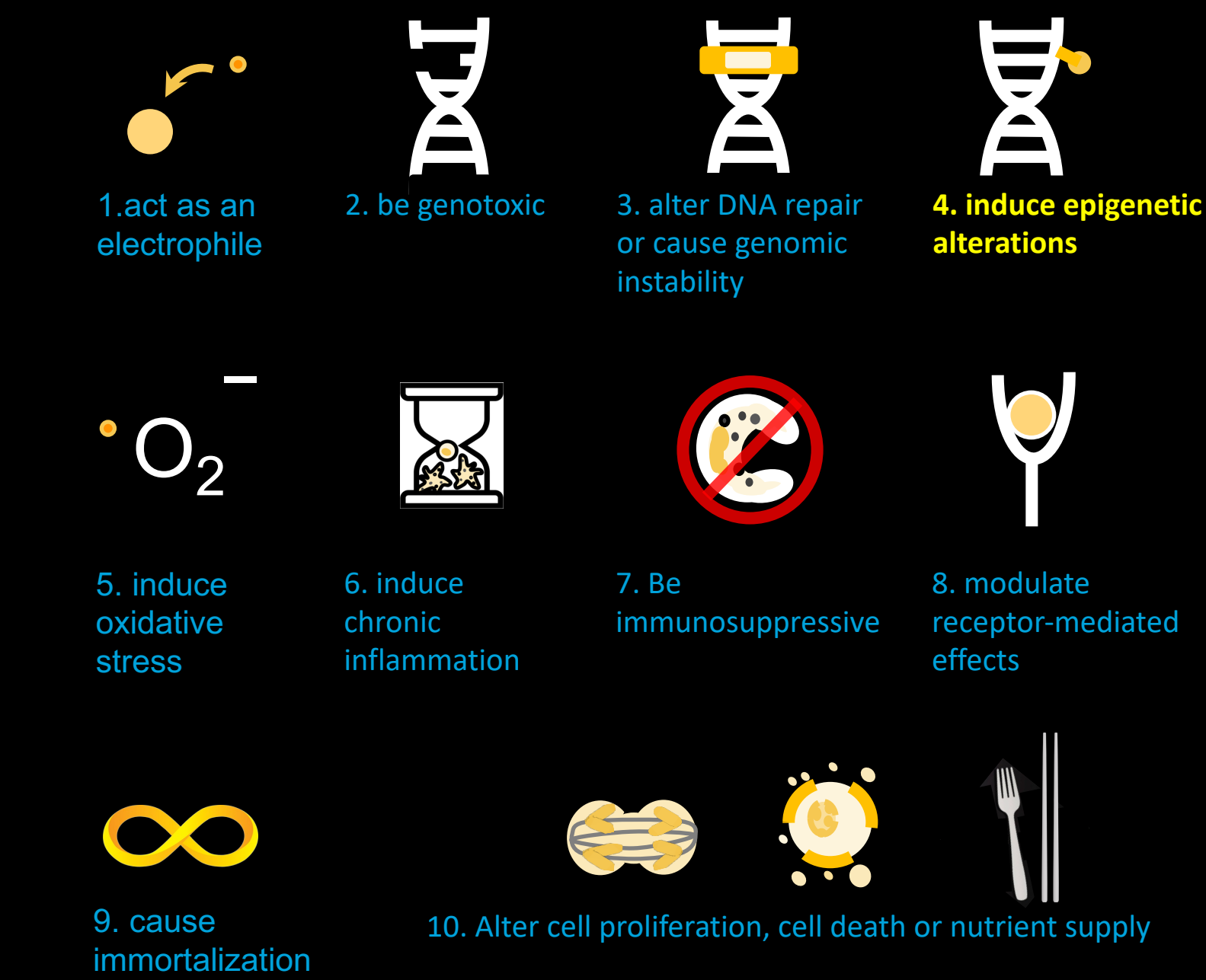


Sandy C. Garner¹, Whitney Arroyave¹, Rachel Kalsch¹, Ruth Lunn², Stan Atwood¹, William Bisson¹, Mukesh Verma³, Amy Wang²

¹Inotiv (formerly Integrated Laboratory Systems), Research Triangle Park, North Carolina ²National Cancer Institute, Bethesda, Maryland, ³Division of the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina

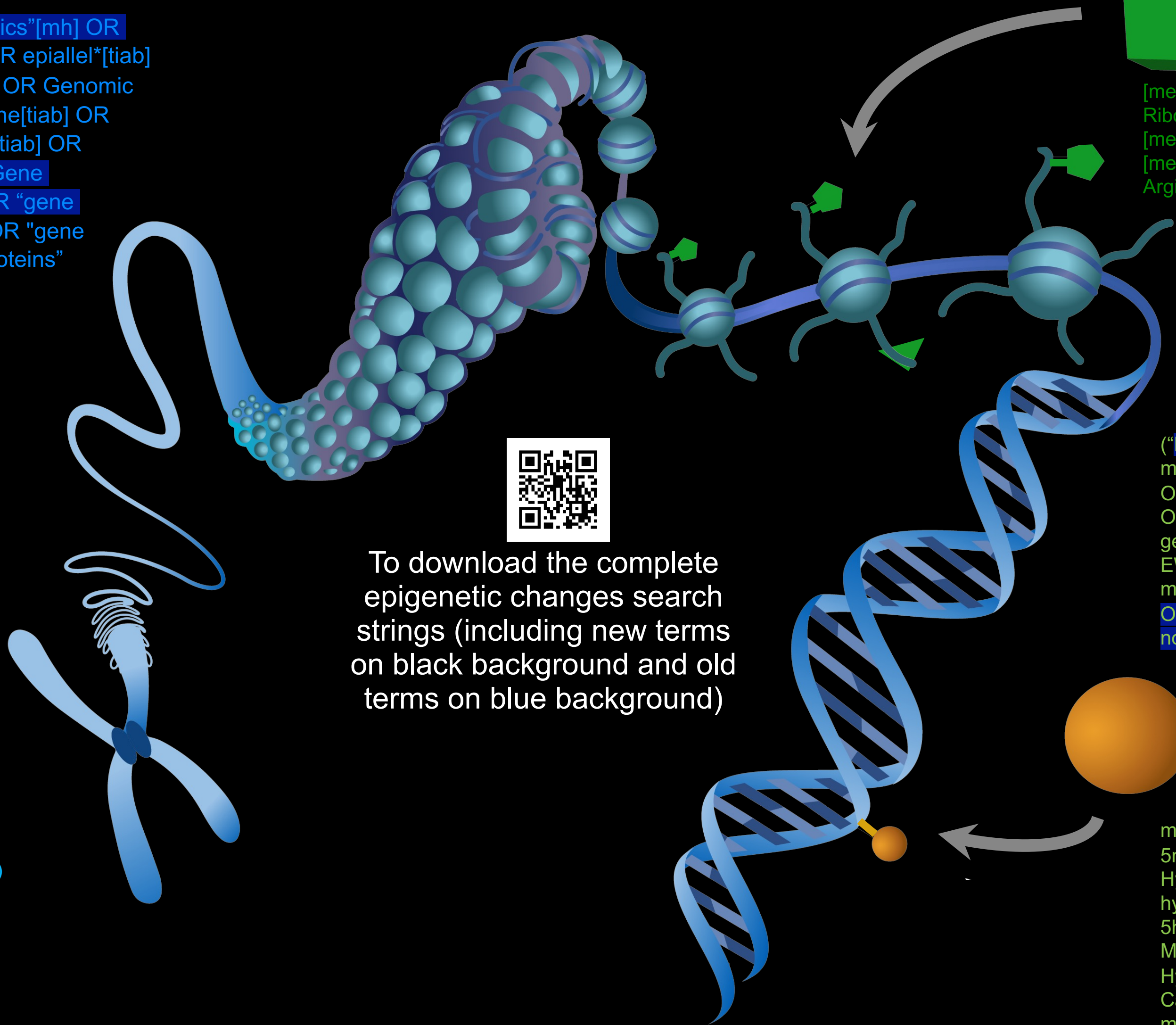
- **Key characteristics of carcinogens (KCCs)** are used for Report on Carcinogens (RoC) hazard evaluations that use systemic review approach to unbiased search and organize mechanistic information.

- Use published reviews of epigenetics methods and research areas to identify the 6 topic areas.
- Develop new search strings in each topic area based on the review articles.
- The topic areas with the largest number of new search terms added were histone modification, chromatin remodeling and organization, and RNA nucleotide modification and methylation.



["Epigenesis, genetic"(mh) OR "Epigenomics"(mh) OR
 "epigen"(tiab) OR epitranscriptome [tiab] OR epiallel [tiab]
 OR epimutat* [tiab] OR "epigenetic mark*" OR Genomic
 imprinting(mh) OR (imprint*[tiab] AND (gene[tiab] OR
 genes[tiab] OR genetic[tiab] OR genomic[tiab] OR
 loc[tiab])) OR dna-modification[tiab] OR Gene
 silencing(mh) OR "gene silencing"[tiab] OR "gene
 silencer"[tiab] OR "gene activation"[tiab] OR "gene
 inactivation"[tiab] OR "Polycomb group proteins"
 OR "PcG silencing")

((([Chromatin][mh] OR chromatin[tiab] OR nucleosome[tiab] AND (remodel*[tiab]) OR [Chromatin-organization][tiab] OR "chromatin modification" OR "open chromatin" OR ("Euchromatin"[MeSH Terms] OR "Euchromatin") OR (open AND "Chromatin"[MeSH Terms] OR "Chromatin")) OR ("Chromatin"[MeSH Terms] OR "Chromatin" OR "Chromatin") AND relax*) OR ("Heterochromatin"[MeSH Terms] OR "Heterochromatin") OR ("Chromatin"[MeSH Terms] OR "Chromatin" AND compact*) OR ("Chromatin"[MeSH Terms] OR "Chromatin" AND condens*) OR ("Heterochromatin"[MeSH Terms] OR "Heterochromatin" AND constitutive*) OR ("Heterochromatin"[MeSH Terms] OR "Heterochromatin" AND facultative*) OR (pericentromere AND DNA) OR (satellite AND DNA) OR (DNA AND "transposable elements") OR (tandem AND repeats) OR (interspersed AND repeats))



OR histone methyltransferase[mh] OR histone methyltransferases[mh] OR histone methyltransferase [mh]
OR histone methyltransferase [mh] OR histone methyltransferase [mh] OR histone methyltransferase [mh]
OR histone* [tiab] AND (methylat*[tiab] OR methylase*[tiab] OR
or hypermethylation[tiab] OR hypomethylation[tiab] OR acetylation[mh] OR
acetylase*[tiab] OR acetylal*[tiab] OR acetyltransferases[mh] OR
acetyltransferase*[tiab] OR acetyl-transferase*[tiab] OR acetylglucosamine
[mh] OR de-acetylal*[tiab] OR HDAC[tiab] OR
deacetylase*[tiab] OR proteasome OR
ubiquitins[mh] OR "phosphorylation" OR phosphorylation [MeSH] OR
"lysine crotonylation" OR lysine [MeSH] OR butyrylation OR butylation OR
propionylation OR ("lysine hydroxylation") OR Tyrosine
[mesh] AND (Hydroxylation [mesh]) OR "biotinylation" OR
Biotin [mesh] OR Biotinylation [mesh] OR
"neddylat[ion]" OR NEDD8 Protein [mesh] OR Sumoylation
[mesh] OR SUMO-1 Protein [Mesh] OR * O-Linked N-
acetylglucosamine* OR *-O-GlcNAc* OR Acetylglucosamine
[mesh] OR N-Acetylglucosaminyltransferases [mesh] OR ((ADP-
Ribosylation [mesh] OR Adenosine Diphosphate) [mesh] AND Ribose
[mesh]) OR ("proline isomerization" OR Proline [mesh]) AND Isomerism
[mesh]) OR "citrullination" OR "imination" OR Citrulline [mesh] OR Protein-
Arginine Deiminases [mesh] OR Citrullination [mesh] OR "N-formylation"))

"DNA Methylation"[mh] OR "DNA Methylation"[tiab] OR "Promoter methylation" OR ((DNA[mh] OR DNA[tiab]) AND (genome, human[mh] OR "genome wide association study"[mh] OR epigenesis, genetic[mh] OR epigenomics[mh] OR genome-wide[tiab] OR GWA5[tiab] OR genome-scale[tiab] OR *Genome[tiab]* OR "epigenome-wide"[tiab] OR EWAS[tiab]) OR "whole genome"[tiab] OR Methylation-profile[tiab] OR methylation-pattern[tiab] OR Methylom[tiab] OR ("CGp islands"[mh] OR CpG[tiab] OR CpGs[tiab] OR CpG5[tiab] OR non-CpG[tiab] OR non-CpG[tiab]) AND (methylat[tiab] OR methylat[tiab] OR methyl[tiab] OR hemimethylat[tiab] OR hypermethylat[tiab] OR nonmethylat[tiab] OR demethylat[tiab] OR unmethylat[tiab] OR remethylat[tiab] OR methyltransferas[tiab] OR "DNA modification methylases"[mh] OR methylas[tiab] OR demethylas[tiab] OR methyltransferase[tiab] OR methyltransferase[tiab] OR 5-methylcytosine[mh] OR "5-methylcytosine"[tiab] OR 5-methyl-cytosine[tiab] OR 5mc[tiab] OR 5mcC[tiab] OR "5 hydroxymethylcytosine"[tiab] OR 5hmC[tiab] OR 5-hydroxymethylat[tiab] OR 5-hydroxymethylcytosine[tiab] OR 5-hydroxy-methylcytosine[tiab] OR 5-hydroxymethyl-cytosine[tiab] OR 5hmC[tiab] OR "5-Formylcytosine" OR "5-Carboxylcytosine" OR Methyladenine [tiab] OR Methylcytosine [tiab] OR 5-hydroxymethylcytosine [tiab] OR Formylcytosine [tiab] OR Carboxylcytosine [tiab] OR methyladenosine OR methylcytosine OR methylguanosine OR (nucleotide[tiab] OR cytosine[mh] OR cytosine[tiab] OR Alu[tiab] OR genes[tiab] OR genom[tiab] AND (methylat[tiab] AND))))

((RNA[mh] OR RNA[tiab]) AND (Queuosine OR Pseudouridine OR Methyladenosine OR Methylcytidine OR Methylguanosine OR Methylinosine OR Methyluridine OR Ribosyladenosine OR Ribosylguanosine OR Formyladenosine OR Formylcytidine OR methylcytosine OR cap methylation OR uridylation OR inosine editing))

["Non-coding RNA/[tiab] OR ncRNA/[tiab] OR [RNA Interference/[mh] OR "Guide RNA" OR "gRNA" OR "Ribonuclease P" OR "Rnase P" OR "Y RNA" OR "Telomerase RNA Component" OR "TERC" OR "Spliced Leader RNA" OR "SL RNA" OR IncRNA/[tiab] OR "iNCNA" OR "RNA, long noncoding" [MeSH] OR "short interfering RNA"/[tiab] OR siRNA/[tiab] OR "small interfering RNA"/[tiab] OR "RNA, Small Interfering" [mh] OR "RNA interference/[mh] OR "small silencing RNA"/[tiab] OR "small inhibitory"/[tiab] OR "small interfering"/[mh] OR "small RNA" OR "smallRNA" OR "small inhibitory RNA"/[tiab] OR microRNAs/[mh] OR miRNA/[tiab] OR microRNA/[tiab] OR "micro RNA"/[tiab] OR "micro RNAs"/[tiab] OR piRNA/[tiab] OR PiwiRNA/[tiab] OR "piwi-interacting RNA"/[tiab] OR "snRNA" OR "small nuclear RNA" OR "splicosomal RNA" OR "snoRNA" OR "small nucleolar RNA" OR "Smy RNA" OR "Small-Cajal-body-specific RNA" OR "scaRNA" OR "RNA editing" OR "RNA splicing" OR "intron retention")]

Purpose:
Compare old and new search terms: to see if the new search terms found articles relevant to epigenetic mechanisms that were not found the old search terms.

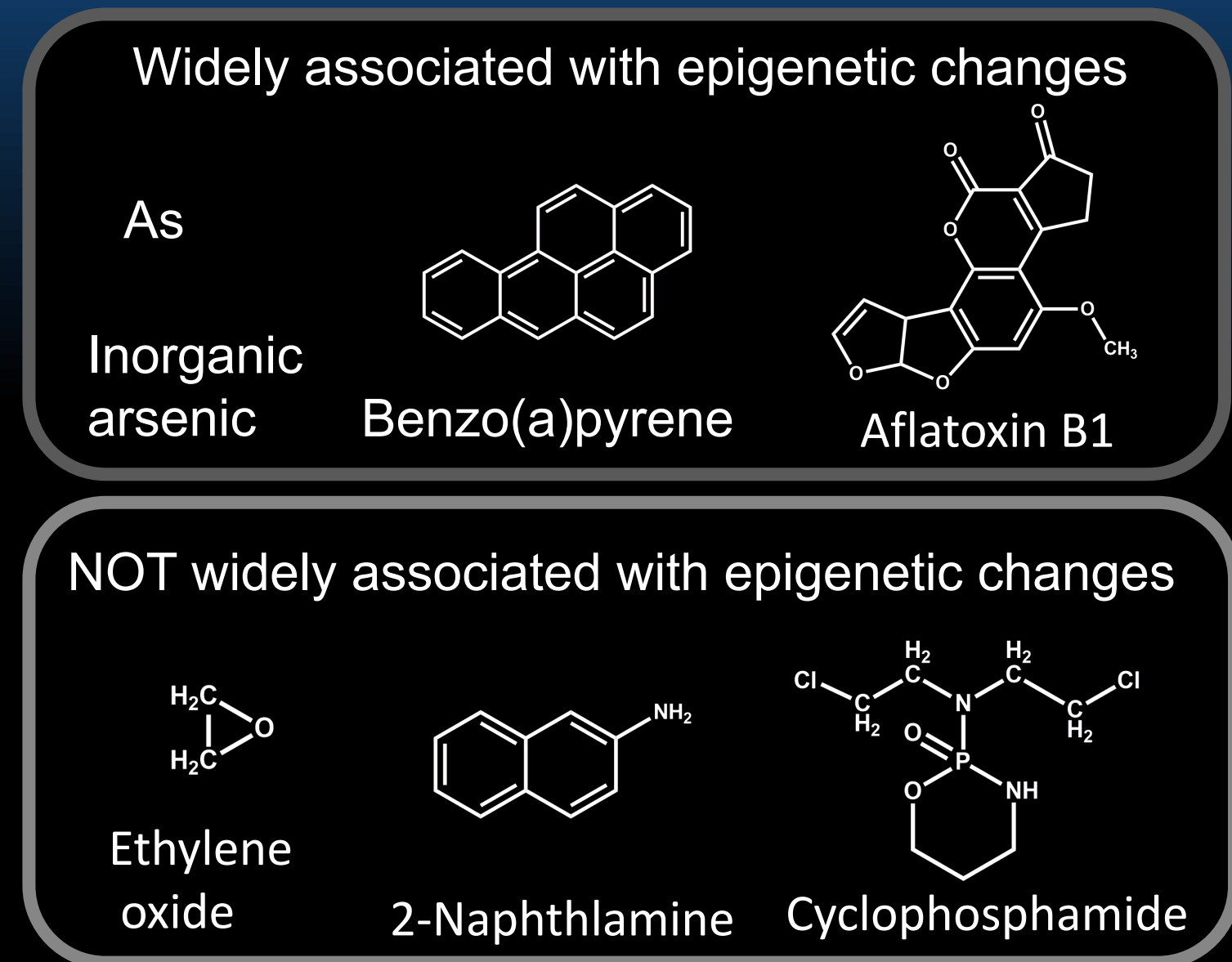
1. Literature search on six chemical carcinogens with both the old and new search terms.
2. Title and abstract screening on up to 50 references per carcinogen and topic.

1. For each epigenetic carcinogen, < 20 to > 600 references were found per topic, and 47%–65% of the references per topic met title abstract screening criteria.

- 71% of references identified through the new search terms and passing title abstract screening met full-text inclusion criteria, showing updated search terms helped identify additional relevant, and likely informative, references.

3. For cyclophosphamide, however, higher than expected number of references (100–200 per topic area) were found for **DNA methylation**, **non-coding RNA** and **RNA silencing**, and **RNA nucleotide modification and methylation**, although the percentage of references meeting title and abstract screening criteria (<30%) was much lower than those for the three epigenetic carcinogens (47%–65%).

- The large increase in epigenetic references that met inclusion criteria indicates **the new search terms are effective at identifying studies on epigenetic mechanisms**.
- These updated epigenetic search terms will be used for all new RoC evaluations.



Topic area	Number of references					New-search-terms-increased references that met screening criteria (%)
	Found	Screened	Screened	Met screening criteria	Met screening criteria	
from search terms	old & new	old only	new only	old only	new only	
3 Carcinogens with epigenetic changes						
Overall/general epigenetics	352	144	6	95	3	3.2
Chromatin remodeling and organization	17	10	7	7	3	42.9
Histone modification	111	55	56	40	17	42.5
DNA methylation	622	128	81	92	6	6.5
Non-coding RNA and RNA silencing	297	154	5	96	3	3.1
RNA nucleotide modification and methylation	9	5	4	3	2	66.7
2 Carcinogens not widely associated with epigenetic changes						
Overall/general epigenetics	16	11	5	0	0	0
Chromatin remodeling and organization	0	0	8	0	0	0
Histone modification	10	2	8	0	0	0
DNA methylation	21	3	18	1	0	0
Non-coding RNA and RNA silencing	21	21	0	0	0	0
RNA nucleotide modification and methylation	0	0	0	0	0	0
Cyclophosphamide						
Overall/general epigenetics	127	76	3	18	1	5.6
Chromatin remodeling and organization	13	5	8	2	3	150
Histone modification	113	27	31	9	2	22.2
DNA methylation	189	41	30	17	3	17.6
Non-coding RNA and RNA silencing	198	79	17	15	2	13.3
RNA nucleotide modification and methylation	1	0	1	0	1	100

