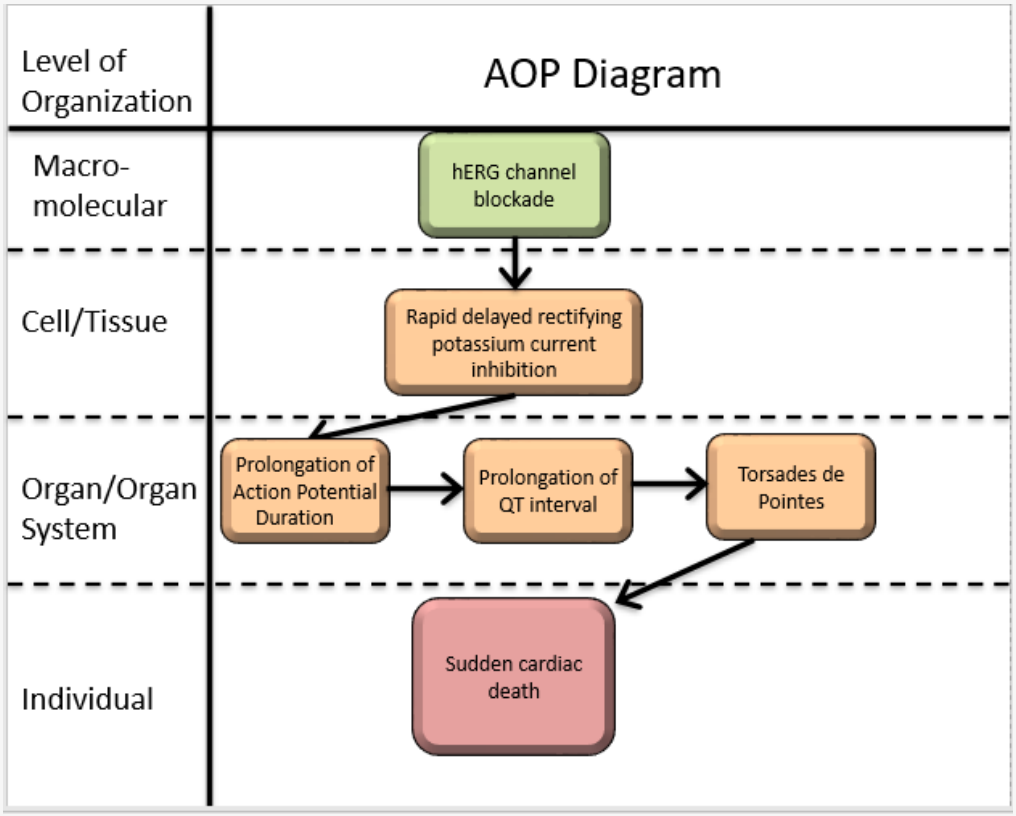
AOP ID and Title:

AOP 433: hERG channel blockade leading to sudden cardiac death
Short Title: From hERG blockade to death

Graphical Representation



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Status

Author status	OECD status	OECD project	SAAOP status
Open for comment. Do not cite			

Abstract

Adverse Outcome Pathways aim to give a precise mechanistic description of relevant toxicological effects. In the current study, an AOP framework is used for increased mortality triggered by drug-mediated blockade of human ether-a-gogo-related gene (hERG) channel. An extensive review of the related scientific literature was conducted for this purpose in order to figure out key events (KEs). The KEs include the inhibition of rapid delayed rectifying potassium current, prolongation of action potential duration, prolongation of QT interval and Torsades de Pointes. Overall, all these steps clearly indicate that there has been a distruption in cardiac electrophysiology, leading to sudden cardiac death on individual level.

AOP development was performed in parallel with OECD guideline. The postulated AOP is expected to serve as the basis for the development of novel drugs with less risk of sudden cardiac death mainly triggered by hERG channel blockade.

Summary of the AOP

Events

Molecular Initiating Events (MIE), Key Events (KE), Adverse Outcomes (AO)

Sequence	Type	Event ID	Title	Short name
	MIE	2099	hERG channel blockade	hERG channel blockade
	KE	2100	Inhibition of rapid delayed rectifying potassium current	Inhibition of rapid delayed rectifying potassium current
	KE	1961	Prolongation of Action Potential Duration	Prolongation of Action Potential
	KE	1962	Prolongation of QT interval	Prolongation of QT interval
	KE	1963	Torsades de Pointes	Torsades de Pointes
	AO	1964	Sudden cardiac death	Sudden cardiac death

Key Event Relationships

Upstream Event	Relationship Type	Downstream Event	Evidence	Quantitative Understanding
hERG channel blockade	adjacent	Inhibition of rapid delayed rectifying potassium current	High	
Inhibition of rapid delayed rectifying potassium current	adjacent	Prolongation of Action Potential Duration	High	
Prolongation of Action Potential Duration	adjacent	Prolongation of QT interval	High	
Prolongation of QT interval	adjacent	Torsades de Pointes	Low	
Torsades de Pointes	adjacent	Sudden cardiac death	Low	

Overall Assessment of the AOP

Domain of Applicability

Life Stage Applicability

Life Stage	Evidence
All life stages	Not Specified

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
human	Homo sapiens	High	NCBI

Sex Applicability

Sex	Evidence
Female	High

Homo sapiens

Considerations for Potential Applications of the AOP (optional)

The AOP may be useful in the risk assessment on several types molecules including drugs, as well as other types of chemicals, biocides, or pesticides. This AOP elucidating the pathway from hERG blockade to sudden cardiac death may provide important insights into the potential toxicity of direct and/or indirect hERG inhibitors.

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Appendix 1

List of MIEs in this AOP

Event: 2099: hERG channel blockade

Short Name: hERG channel blockade

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:433 - hERG channel blockade leading to sudden cardiac death	MolecularInitiatingEvent

Biological Context

Level of Biological Organization
Molecular

List of Key Events in the AOP

Event: 2100: Inhibition of rapid delayed rectifying potassium current

Short Name: Inhibition of rapid delayed rectifying potassium current

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:433 - hERG channel blockade leading to sudden cardiac death	KeyEvent

Biological Context

Level of Biological Organization
Cellular

Event: 1961: Prolongation of Action Potential Duration

Short Name: Prolongation of Action Potential

AOPs Including This Key Event

AOP ID and Name	Event Type

AOP ID and Name	Event Type
Aop:433 - hERG channel blockade leading to sudden cardiac death	KeyEvent

Biological Context

Level of Biological Organization
Organ

Event: 1962: Prolongation of QT interval

Short Name: Prolongation of QT interval

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:433 - hERG channel blockade leading to sudden cardiac death	KeyEvent

Biological Context

Level of Biological Organization
Organ

Event: 1963: Torsades de Pointes

Short Name: Torsades de Pointes

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:433 - hERG channel blockade leading to sudden cardiac death	KeyEvent

Biological Context

Level of Biological Organization
Organ

List of Adverse Outcomes in this AOP

Event: 1964: Sudden cardiac death

Short Name: Sudden cardiac death

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:433 - hERG channel blockade leading to sudden cardiac death	AdverseOutcome

Biological Context

Level of Biological Organization
Individual

Appendix 2

List of Key Event Relationships in the AOP

List of Adjacent Key Event Relationships

Relationship: 2850: hERG channel blockade leads to Inhibition of rapid delayed rectifying potassium current

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
hERG channel blockade leading to sudden cardiac death	adjacent	High	

Relationship: 2851: Inhibition of rapid delayed rectifying potassium current leads to Prolongation of Action Potential

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
hERG channel blockade leading to sudden cardiac death	adjacent	High	

Relationship: 2540: Prolongation of Action Potential leads to Prolongation of QT interval

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
hERG channel blockade leading to sudden cardiac death	adjacent	High	

Relationship: 2541: Prolongation of QT interval leads to Torsades de Pointes

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
hERG channel blockade leading to sudden cardiac death	adjacent	Low	

Relationship: 2542: Torsades de Pointes leads to Sudden cardiac death

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
hERG channel blockade leading to sudden cardiac death	adjacent	Low	