AOP ID and Title:

SNAPSHOT

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AOP 163: PPARgamma activation leading to sarcomas in rats, mice, and hamsters

Short Title: PPARgamma-related sarcomas

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Status

Author status	OECD status	OECD project	SAAOP status
Under development: Not open for comment. Do not cite		1.29	Under Development

Abstract

This putative adverse outcome pathway (AOP) outlines potential key events leading to a tumor outcome in standard carcinogenicity models. This information is based largely on modes of action described previously in cited literature sources and is intended as a resource template for AOP development and data organization. Presentation in this Wiki does not indicate EPA acceptance of a particular pathway for a given reference agent, only that the information has been proposed in some manner. In addition, this putative AOP relates to the model species indicated and does not directly address issues of human relevance.

Summary of the AOP

Events

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

Sequence	Type	Event ID	Title	Short name
1	MIE	1028	Activation of specific nuclear receptors, PPAR-gamma activation (https://aopwiki.org/events/1028)	Activation of specific nuclear receptors, PPAR-gamma activation
2	KE	1029	Increased, adipogenesis (https://aopwiki.org/events/1029)	Increased, adipogenesis
3	KE	1032	Increased, secretion of local growth factors (https://aopwiki.org/events/1032)	Increased, secretion of local growth factors
4	KE	1033	Increased, proliferation of mesenchymal cells (https://aopwiki.org/events/1033)	Increased, proliferation of mesenchymal cells
5	KE	1034	Increased, IGF-1 (mouse) (https://aopwiki.org/events/1034)	Increased, IGF-1 (mouse)
6	KE	1035	Increased, Firbrosarcoma (https://aopwiki.org/events/1035)	Increased, Firbrosarcoma
7	KE	1036	Increased, liposarcoma (https://aopwiki.org/events/1036)	Increased, liposarcoma

Sequence	Type	Event ID	Title	Short name
8	KE	1037	Increased, hemagiosarcoma (https://aopwiki.org/events/1037)	Increased, hemagiosarcoma

Key Event Relationships

Upstream Event	Relationship Type	Downstream Event	Evidence	Quantitative Understanding
Increased, adipogenesis (https://aopwiki.org/relationships/1073)	adjacent	Increased, secretion of local growth factors	High	
Increased, secretion of local growth factors (https://aopwiki.org/relationships/1074)	adjacent	Increased, proliferation of mesenchymal cells	High	
Increased, secretion of local growth factors (https://aopwiki.org/relationships/1075)	adjacent	Increased, IGF-1 (mouse)	High	
Increased, proliferation of mesenchymal cells (https://aopwiki.org/relationships/1076)	adjacent	Increased, Firbrosarcoma	High	
Increased, proliferation of mesenchymal cells (https://aopwiki.org/relationships/1077)	adjacent	Increased, liposarcoma	High	
Increased, proliferation of mesenchymal cells (https://aopwiki.org/relationships/1078)	adjacent	Increased, hemagiosarcoma	High	
Activation of specific nuclear receptors, PPAR-gamma activation (https://aopwiki.org/relationships/1071)	non-adjacent	Increased, adipogenesis	High	
Activation of specific nuclear receptors, PPAR-gamma activation (https://aopwiki.org/relationships/1072)	non-adjacent	Increased, secretion of local growth factors	Moderate	

Stressors

Name	Evidence
Troglitazone	

Overall Assessment of the AOP

Domain of Applicability

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
Rattus rattus	Rattus rattus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10117)
mouse	Mus musculus	Moderate	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10090)

References

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Appendix 1

List of MIEs in this AOP

Event: 1028: Activation of specific nuclear receptors, PPAR-gamma activation (https://aopwiki.org/events/1028)

Short Name: Activation of specific nuclear receptors, PPAR-gamma activation

Key Event Component

Process	Object	Action
peroxisome proliferator activated receptor signaling pathway	peroxisome proliferator-activated receptor gamma	decreased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:163 - PPARgamma activation leading to sarcomas in rats, mice, and hamsters (https://aopwiki.org/aops/163)	MolecularInitiatingEvent
Aop:72 - Epigenetic modification of PPARG leading to adipogenesis (https://aopwiki.org/aops/72)	KeyEvent

Stressors

Name
Tetrabromobisphenol A

Biological Context

Level of Biological Organization
Molecular

Cell term

Cell term
hepatocyte

Evidence for Perturbation by Stressor

Tetrabromobisphenol A

TBBPA binds to PPARγ *in vitro*, with a Kd of 0.78 µM and *in vivo* in zebrafish, with a LOEL of 100 nM (Fang et al., 2015; Riu et al., 2011; Riu et al., 2014). Mild activation has also been reported *in vitro* in several research papers and in ToxCast assays as well, with effective doses ranging from 0.3 to 10 µM (Riu et al., 2011; Riu et al., 2014; Suzuki et al., 2013; ToxCastTM Data; Watt and Schlezinger, 2015).

List of Key Events in the AOP

Event: 1029: Increased, adipogenesis (https://aopwiki.org/events/1029)

Short Name: Increased, adipogenesis

Key Event Component

Process	Object	Action
fat cell differentiation		increased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:163 - PPARgamma activation leading to sarcomas in rats, mice, and hamsters (https://aopwiki.org/aops/163)	KeyEvent

Biological Context

Level of Biological Organization
Cellular

Cell term

Cell term
eukaryotic cell

Event: 1032: Increased, secretion of local growth factors (https://aopwiki.org/events/1032)

Short Name: Increased, secretion of local growth factors

Key Event Component

Process	Object	Action
secretion	eukaryotic protein	increased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:163 - PPARgamma activation leading to sarcomas in rats, mice, and hamsters (https://aopwiki.org/aops/163)	KeyEvent
Aop:171 - Chronic cytotoxicity of the serous membrane leading to pleural/peritoneal mesotheliomas in the rat. (https://aopwiki.org/aops/171)	KeyEvent

Biological Context

Level of Biological Organization
Cellular

Cell term

Cell term
eukaryotic cell

Event: 1033: Increased, proliferation of mesenchymal cells (https://aopwiki.org/events/1033)

Short Name: Increased, proliferation of mesenchymal cells

Key Event Component

Process	Object	Action
mesenchymal cell proliferation	mesenchymal cell	increased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:163 - PPARgamma activation leading to sarcomas in rats, mice, and hamsters (https://aopwiki.org/aops/163)	KeyEvent

Biological Context

Level of Biological Organization
Cellular

Cell term

Cell term
mesenchymal cell

Event: 1034: Increased, IGF-1 (mouse) (https://aopwiki.org/events/1034)

Short Name: Increased, IGF-1 (mouse)

Key Event Component

Process	Object	Action
gene expression	IGF-like family receptor 1 (mouse)	increased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:163 - PPARgamma activation leading to sarcomas in rats, mice, and hamsters (https://aopwiki.org/aops/163)	KeyEvent

Biological Context

Level of Biological Organization
Cellular

Cell term

Cell term
eukaryotic cell

Event: 1035: Increased, Firbrosarcoma (https://aopwiki.org/events/1035)

Short Name: Increased, Firbrosarcoma

Key Event Component

Process	Object	Action
	Fibrosarcoma	increased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:163 - PPARgamma activation leading to sarcomas in rats, mice, and hamsters (https://aopwiki.org/aops/163)	KeyEvent

Biological Context

Level of Biological Organization
Tissue

Organ term

Organ term
fibrous connective tissue

Event: 1036: Increased, liposarcoma (https://aopwiki.org/events/1036)

Short Name: Increased, liposarcoma

Key Event Component

Process	Object	Action
	liposarcoma	increased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:163 - PPARgamma activation leading to sarcomas in rats, mice, and hamsters (https://aopwiki.org/aops/163)	KeyEvent

Biological Context

Level of Biological Organization
Tissue

Organ term

Organ term
adipose tissue

Event: 1037: Increased, hemagiosarcoma (https://aopwiki.org/events/1037)

Short Name: Increased, hemagiosarcoma

Key Event Component

Process	Object	Action
	hemangiosarcoma	increased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:163 - PPARgamma activation leading to sarcomas in rats, mice, and hamsters (https://aopwiki.org/aops/163)	KeyEvent

Biological Context

Level of Biological Organization
Tissue

Organ term

Organ term
blood vessel endothelium

Appendix 2

List of Key Event Relationships in the AOP

List of Adjacent Key Event Relationships

Relationship: 1073: Increased, adipogenesis leads to Increased, secretion of local growth factors (https://aopwiki.org/relationships/1073)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
PPARgamma activation leading to sarcomas in rats, mice, and hamsters (https://aopwiki.org/aops/163)	**adjacent**	**High**	

Relationship: 1074: Increased, secretion of local growth factors leads to Increased, proliferation of mesenchymal cells (https://aopwiki.org/relationships/1074)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
PPARgamma activation leading to sarcomas in rats, mice, and hamsters (https://aopwiki.org/aops/163)	**adjacent**	**High**	

Relationship: 1075: Increased, secretion of local growth factors leads to Increased, IGF-1 (mouse) (https://aopwiki.org/relationships/1075)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
PPARgamma activation leading to sarcomas in rats, mice, and hamsters (https://aopwiki.org/aops/163)	**adjacent**	**High**	

Relationship: 1076: Increased, proliferation of mesenchymal cells leads to Increased, Firbrosarcoma (https://aopwiki.org/relationships/1076)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
PPARgamma activation leading to sarcomas in rats, mice, and hamsters (https://aopwiki.org/aops/163)	**adjacent**	**High**	

Relationship: 1077: Increased, proliferation of mesenchymal cells leads to Increased, liposarcoma (https://aopwiki.org/relationships/1077)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
PPARgamma activation leading to sarcomas in rats, mice, and hamsters (https://aopwiki.org/aops/163)	**adjacent**	**High**	

Relationship: 1078: Increased, proliferation of mesenchymal cells leads to Increased, hemagiosarcoma (https://aopwiki.org/relationships/1078)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
PPARgamma activation leading to sarcomas in rats, mice, and hamsters (https://aopwiki.org/aops/163)	**adjacent**	**High**	

List of Non Adjacent Key Event Relationships

Relationship: 1071: Activation of specific nuclear receptors, PPAR-gamma activation leads to Increased, adipogenesis (https://aopwiki.org/relationships/1071)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
PPARgamma activation leading to sarcomas in rats, mice, and hamsters (https://aopwiki.org/aops/163)	**non-adjacent**	**High**	

Relationship: 1072: Activation of specific nuclear receptors, PPAR-gamma activation leads to Increased, secretion of local growth factors (https://aopwiki.org/relationships/1072)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
PPARgamma activation leading to sarcomas in rats, mice, and hamsters (https://aopwiki.org/aops/163)	**non-adjacent**	**Moderate**	