

Molecular Basis for Tumor Formation by Acrylamide

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Hormonal Tumor Formation

- Leydig cell tumors/TVMs
- Mammary gland fibroadenomas
- Thyroid cell follicular cell adenomas

Tunica Vaginalis Mesotheliomas

	Step in MOA	Degree of Certainty	Relevance to Humans
1	Acrylamide modulates dopamine activity in rats.	Certain. Acrylamide modifies dopamine uptake and release and increases activity of D2 receptors.	Unknown.
2	Pituitary senses increased dopamine signal (TIDA neuron).	Certain.	Uncertain. Aging process is different in humans than rats.
3	Increases in the dopamine signal results in decrease in serum prolactin in aging male rat.	Certain. Serum prolactin levels decrease in rats.	Unknown.
4	Down regulation of LH receptors results in decreased in testosterone levels.	Certain. Testosterone levels drop precipitously.	Not relevant. Human LH receptors are not responsive to prolactin.
5	A compensatory increase in LH from brain caused by decrease in testosterone up-regulates the receptors causing Leydig cell hyperplasia and Leydig cell tumors.	Certain. This mode of action is well documented in Fischer rats.	Not relevant. Rat specific.

Tunica Vaginalis Mesotheliomas

	Step in MOA	Degree of Certainty	Relevance to Humans
6	Production of LC tumors is causally related to the production of TVMs by a hormonal mode: Decreases in testosterone in the peritesticular area alters localized growth factors, especially TGF-beta, which stimulate mesothelial tissues.	Reasonably certain: Evidence for altered expression of growth factors in transformed mesothelial cells.	Not relevant. Fischer 344 rat-specific.
7	Production of LC tumors is causally related to the production of TVMs by a solid state mode.	Good evidence. Size of Leydig cell tumor correlated with TVMs. (<25% testes, no TVMs; >75% all tumors) and the location is where weight-bearing effects would take place.	Not relevant to humans. Architecture and anatomy different in aging Fischer 344 rat.
8	TVMs appear in the chronic Studies in rats.	Certain. Fischer 344 male rat specific. Several other chemicals that produce TVMs in F344 rats did not produce them in strains of rats.	Not relevant. These tumors are very rare in humans.

Mammary Gland Tumors

	Step in MOA	Degree of Certainty	Relevance to Humans
1	Acrylamide modulates dopamine activity in rats	Certain. (See above.)	Unknown.
2	Aging female Fischer 344 rat is refractory to dopamine released from TIDA neurons near the pituitary.	Certain.	Not relevant.
3	Prolactin levels increase in the aging female Fischer 344 rat.	Certain.	Not relevant.
4	Sustained increased prolactin maintains the corpora lutea resulting in increased levels of progesterone.	Certain.	Not relevant.
5	Aging female Fischer 344 rats enter a state of repetitive pseudo-pregnancy.	Certain.	Not relevant.

Mammary Gland Tumors

	Step in MOA	Degree of Certainty	Relevance to Humans
6	Dopamine in female F344 rats is involved in steroidogenesis.	Certain. Ovarian cells contain dopamine receptors and dose-related increases in progesterone with decrease in estrogen when ovarian cells incubated with dopamine (D1) receptor agonists and cAMP levels increased .	Not relevant.
7	Acrylamide modulates dopamine signal (D1 receptors) at the corpora lutea contributing enhancing the background incidence in fibroadenomas in aging F344 female rats.	Uncertain. Evidence is indirect.	Likely not relevant.
8	Increase in mammary fibroadenomas occurs in the end of the study.	Certain.	Not relevant.

Thyroid Gland Tumors

	Step in MOA	Degree of Certainty	Relevance to Humans
1	Normal thyroid function and modes of thyroid tumor formation are well known- modulation of TSH and/or thyroid hormones.	Certain. (See above.)	Relevant.
2	Acrylamide produces a TSH-like response.	Certain. Decreased colloid area and increased thyroid follicular cell height and some changes in T4 and T3 levels at very high doses in 28-day study.	Relevant. Similar physiology.
3	Acrylamide caused increased cell proliferation and DNA synthesis in the thyroid but not the liver.	Certain.	Not relevant. Huge goiters do not relate to tumors.
4	Potential signal interference involving a second messenger system, cAMP, is a likely candidate.	Uncertain. Effects of TSH in rat thyroid cells is primarily mediated by cAMP and D1 agonist increase cAMP activity (see above).	Unknown.
5	Literature supports a non-genotoxic mechanism	Virtually no chemical causes thyroid cancer in rats by genotoxic mechanism.	Not relevant. No chemical has caused thyroid cancer in man.