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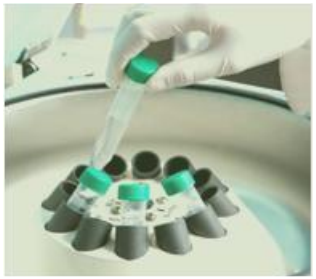



Glyphosate Review

OEHHA Meeting
October 7

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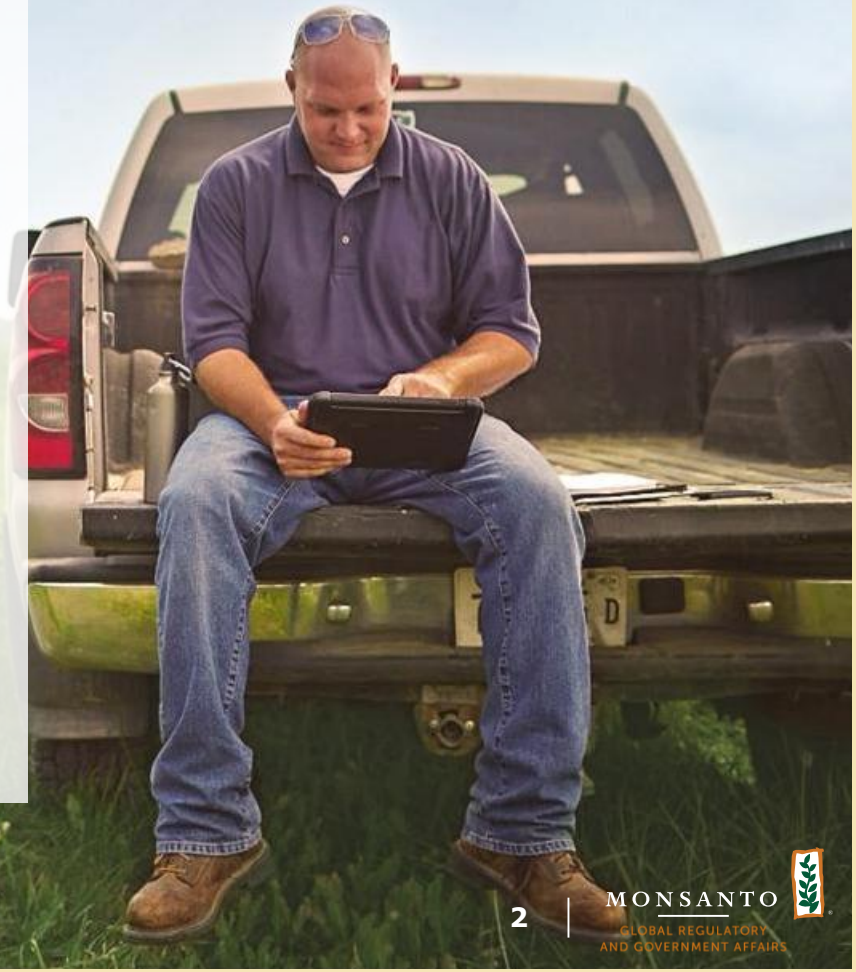
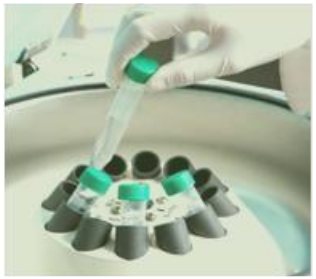
Agenda

- Importance of glyphosate use in California
- History of glyphosate safety reviews
- Evaluation of the NSRL for glyphosate







Importance of Glyphosate Uses in California

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Vegetation and Weed Management

Broad Utilization

- Glyphosate is an established and important vegetation management tool used by highly trained and certified California pesticide applicators in an integrated vegetation management system because it is cost-effective, essentially non-toxic to birds, fish, and mammals.
- Farmers in CA use glyphosate to provide a weed free seed bed using pre-plant applications where conservation tillage practices are utilized to improve surface water quality and soil health.

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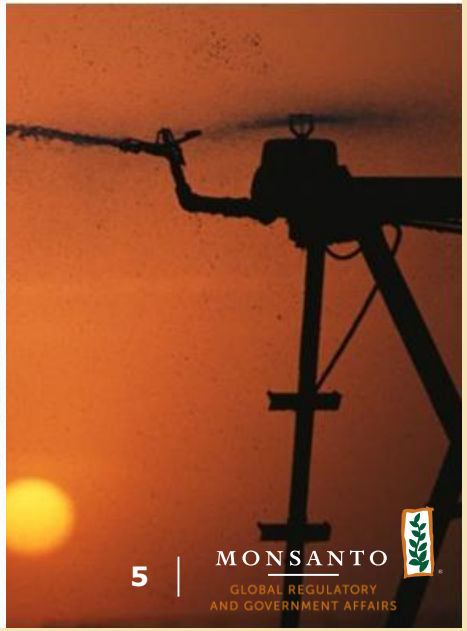
Vegetation and Weed Management

Broad Utilization

- Glyphosate is widely used by government agencies in CA to control vegetation and establish fire breaks during the wet months of the year. This helps municipalities and other government agencies protect valuable resources, property and the public from the uncontrolled spread of wildfires in California.
- Vegetation management in sources of drinking water will be negatively impacted if glyphosate can't be used



Vegetation and Weed Management

Broad Utilization

Municipal, county, and state agencies have a limited budget for vegetation management which could be negatively affected in the following ways:

- Vegetation management in irrigation, water transport canals, along roadsides around buildings, bridges and other infrastructure will be more difficult and require more costly management practices.
- Ditch banks, steep hillsides and many non-crop areas are not assessable with heavy equipment or mowers increasing the risk of injury for workers who must frequently re-enter the area to maintain mechanical control of tall growing vegetation.

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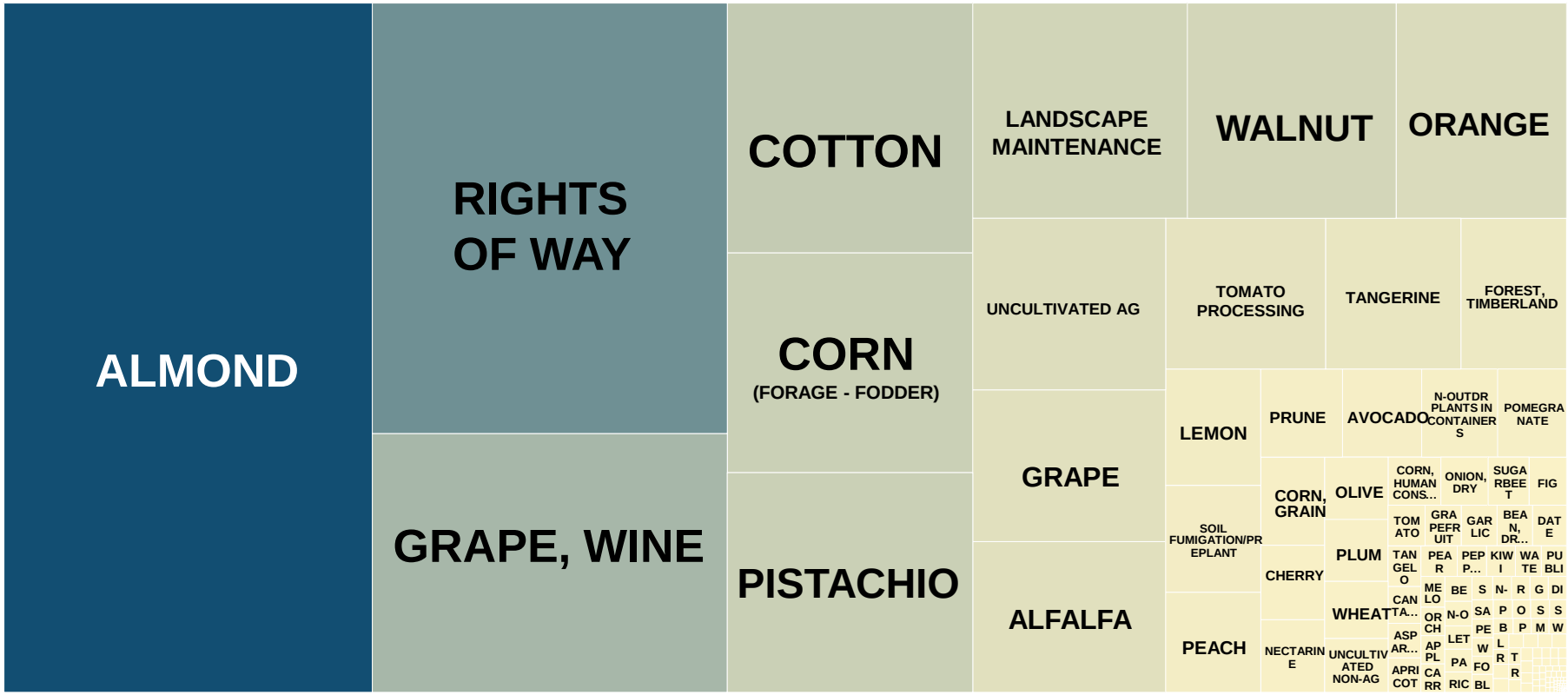
Glyphosate Uses – 2013 Data only

Relative importance based on use



Summary of Pesticide Use Report Data – 2013. California Department of Pesticide Regulation – Brian Leahy.

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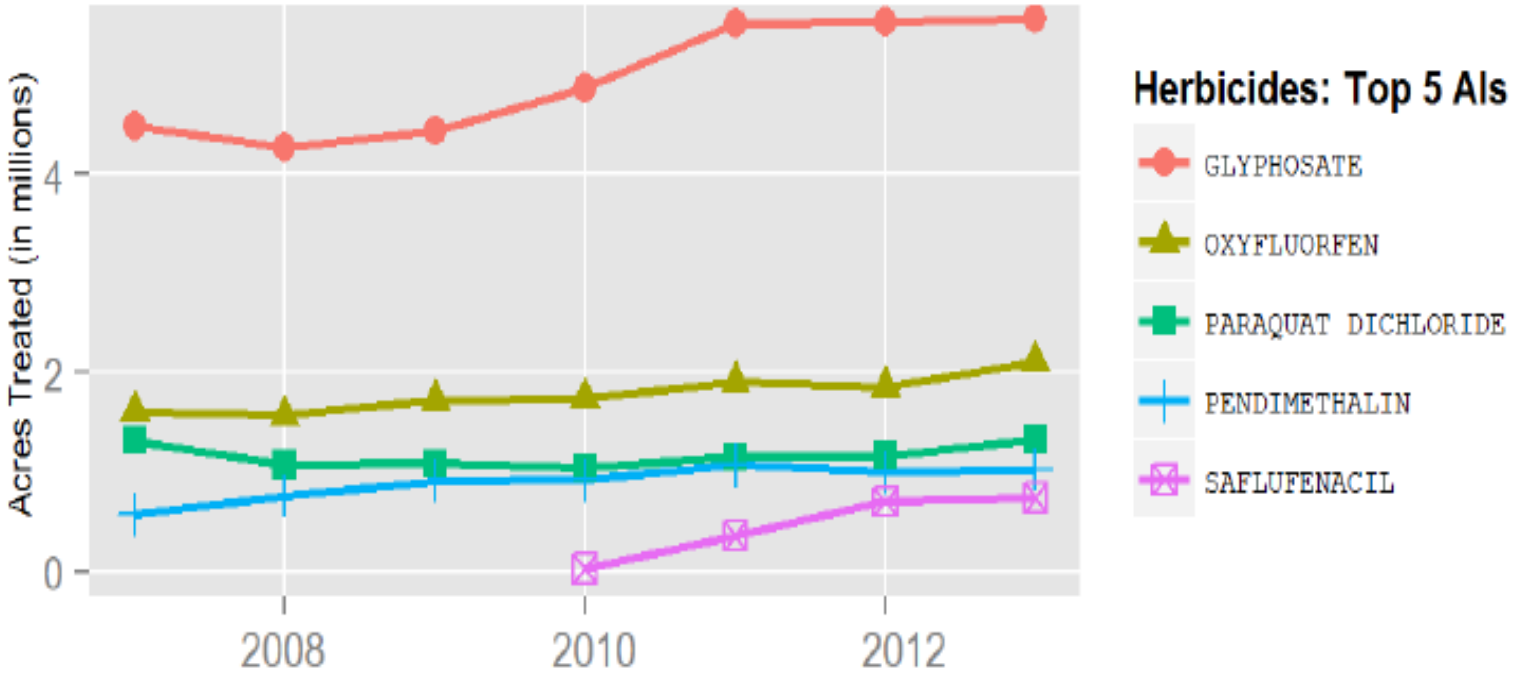
Top 5 Active Ingredients

Total for all crops in California



Summary of Pesticide Use Report Data 2009–2013. California Department of Pesticide Regulation – Brian Leahy.

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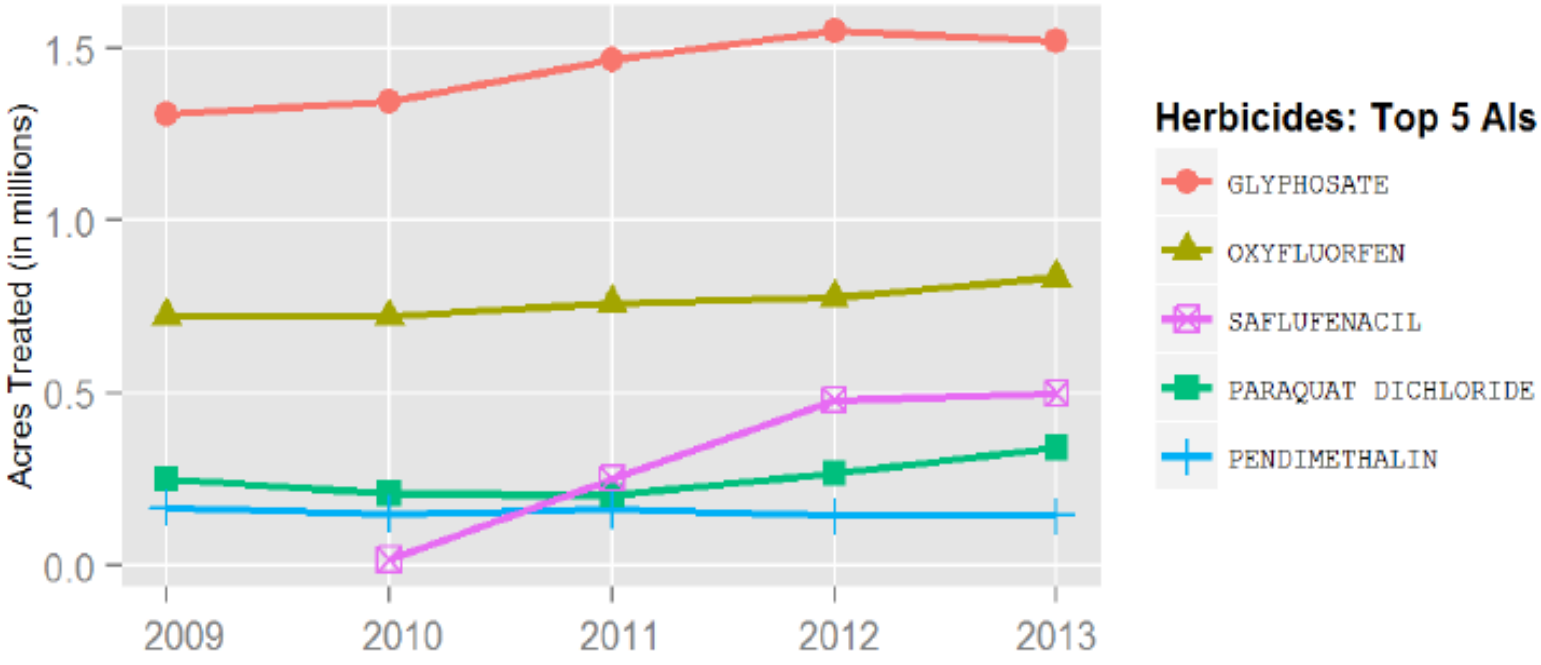
Top 5 Active Ingredients

Total use in Almonds



Summary of Pesticide Use Report Data 2009–2013. California Department of Pesticide Regulation – Brian Leahy.

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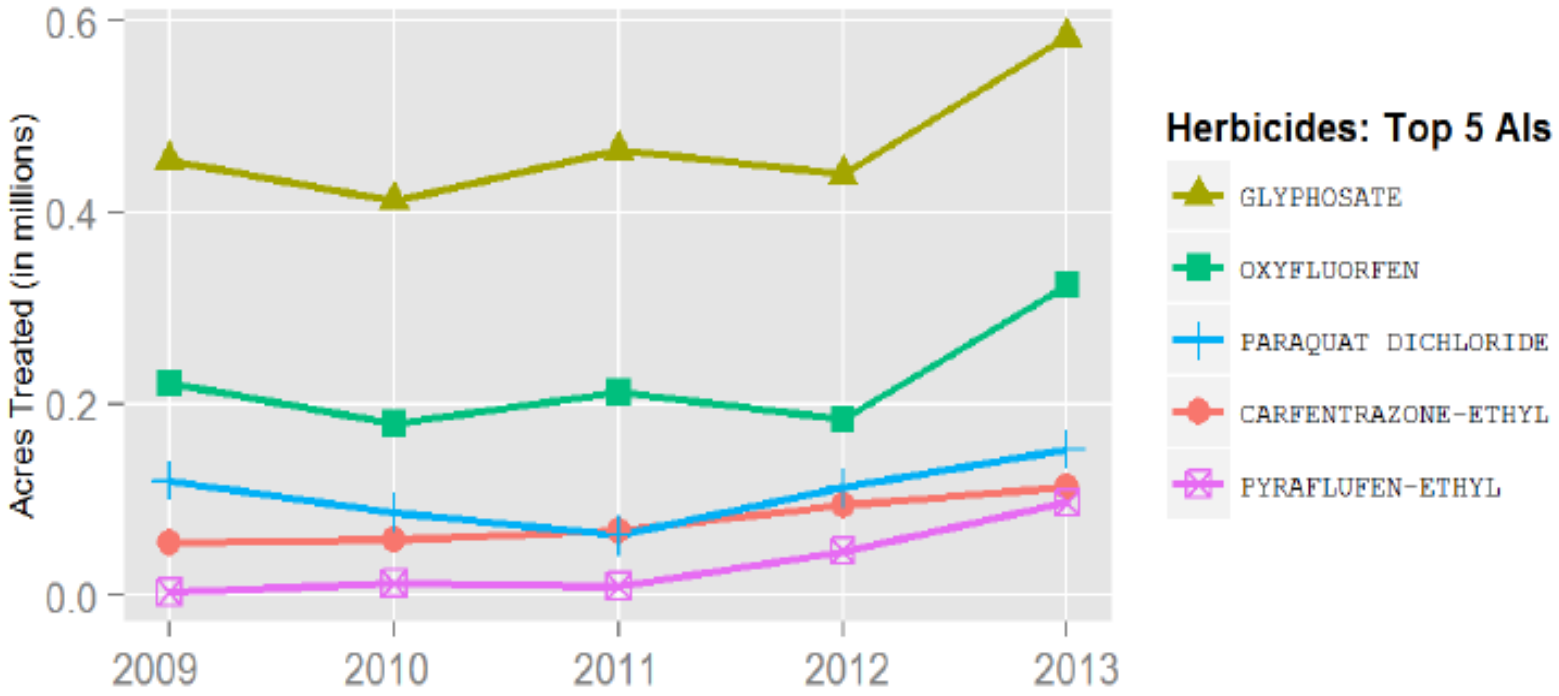
Top 5 Active Ingredients

Total Use in Wine Grapes



Summary of Pesticide Use Report Data 2009–2013. California Department of Pesticide Regulation – Brian Leahy.

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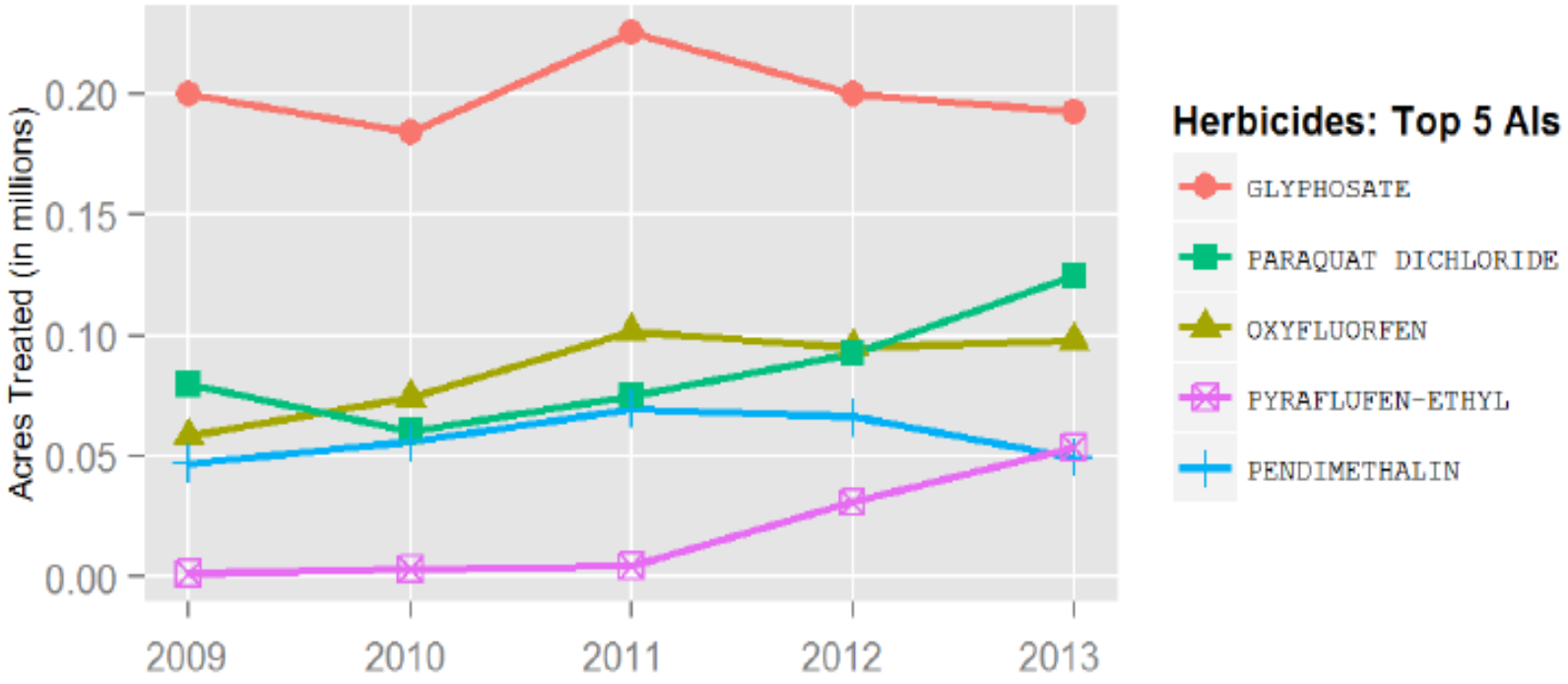
Top 5 Active Ingredients

Total Use in Table and Raisin Grapes



Summary of Pesticide Use Report Data 2009–2013. California Department of Pesticide Regulation – Brian Leahy.

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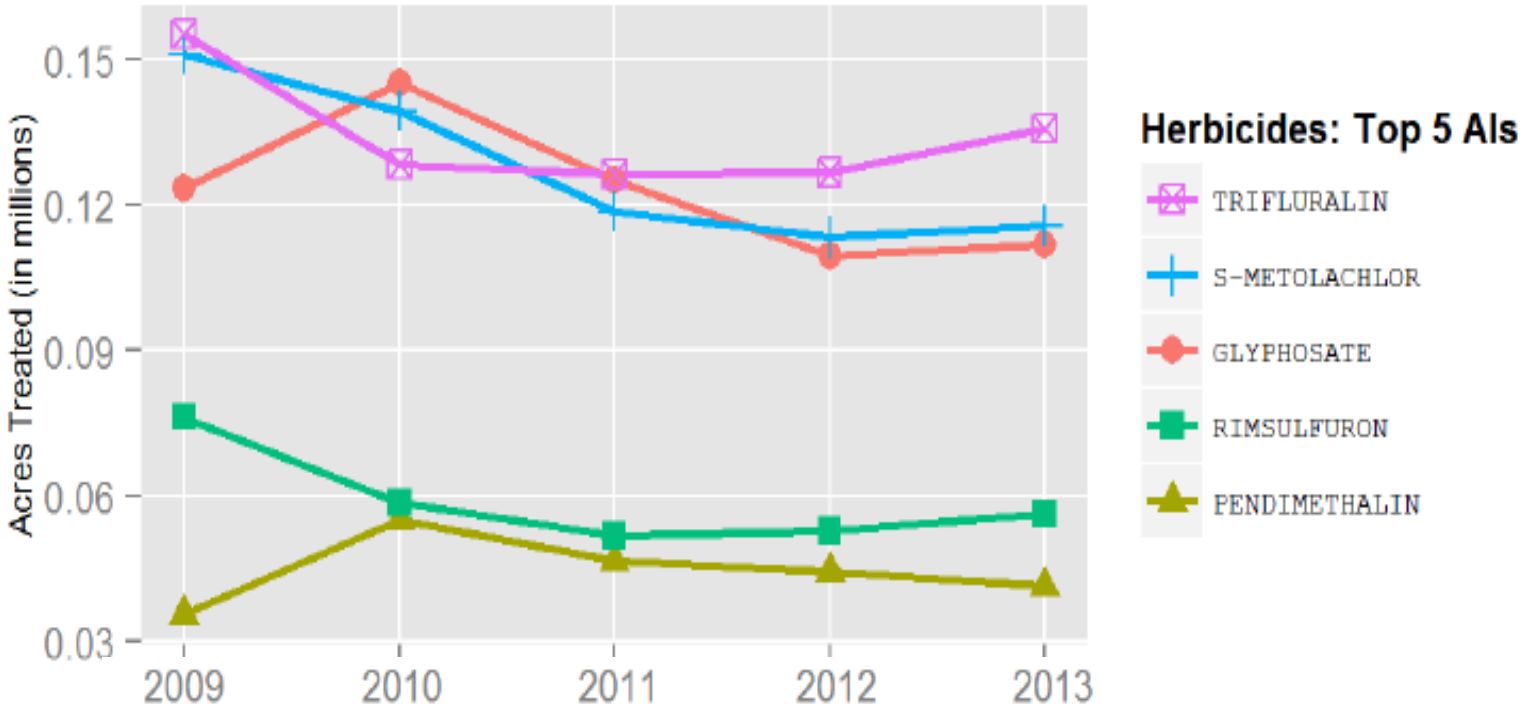
Top 5 Active Ingredients

Total Use in Processing Tomatoes



Summary of Pesticide Use Report Data 2009–2013. California Department of Pesticide Regulation – Brian Leahy.

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Alternative Product Comparison

If glyphosate can't be used

Product	Signal Word	REI (hrs)	Pre/Post	Comments
Glyphosate	Caution	4	Post	Broad spectrum weed control (surfactant in some formulas is toxic to fish)
Oxyfluorfen	Caution	24 - 48	Pre/Post	Toxic to aquatic invertebrates and wildlife
Paraquat	Danger	12	Post	Broad spectrum weed control, Acutely toxic, toxic to wildlife
Pendimethalin	Caution	24	Pre	Grasses and some dicots, Toxic to fish
Saflufenacil	Caution	12	Post/Pre	Dicots, High potential to reach surface water several weeks after application
Carfentrazone	Caution	12	Post	Dicots, toxic to fish
Pyraflufen	Caution	12	Post	Dicots, toxic to fish and aquatic invertebrates
Hexazinone	Danger	48	Pre/Post	Irreversible eye damage

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History Of Glyphosate Safety Reviews

1974, Monsanto commercialized a new herbicide called Roundup®.

The active ingredient in the herbicide is glyphosate. A majority of Roundup brand herbicides contain three major components – the active ingredient glyphosate, water and a soap-like surfactant blend.

The herbicide was developed to control a wide variety of unwanted vegetation.

Over the years, various formulations of Roundup brand products and other glyphosate-based herbicides have been developed by Monsanto and other companies, and these formulations are used throughout the world by farmers, landowners and homeowners.

History of Global Uses:

1974 – Control of perennial and annual weeds in non-crop and industrial areas.

1976 – Perennial weed control in perennial crops and before planting or following harvest of annual crops with first crop use label.

1978 – Spot spraying of perennial weeds in annual crops like cotton and soybeans.

1979 – Selective application in annual crops with re-circulating sprayers or rope wick applicators for control of annual and perennial weeds.

1986 – Control of annual weeds prior to planting annual crops in reduced or no-tillage systems.

1996 – Introduction of Roundup Ready® technology, which permitted direct application for weed control in glyphosate-tolerant crops.

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	Tumors related to treatment?	MON Mouse	MON Rat 1	MON Rat 2	CHEM Mouse
2015	WHO/IARC	Yes	Yes	Yes	Yes

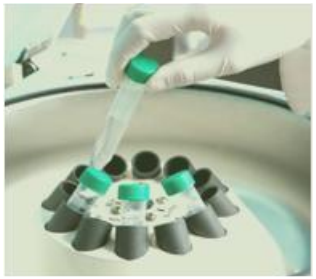
	Tumors related to treatment?	MON Mouse	MON Rat 1	MON Rat 2	CHEM Mouse
2015	WHO/IARC	Yes	Yes	Yes	Yes
1987	WHO/JMPR				
1991	US EPA Cancer Classification				
1991	Canada PMRA				
1993	US EPA RED				
1994	WHO/IPCS				
1999	Japan FCS				
2000	FAO Specifications				
2002	EU Annex I				
2004	WHO/JMPR				
2005	WHO/Water Sanitation Health				
2007	OEHHA				
2007	Brazil Anvisa*				
2008	US EPA Effects Determination				
2010	Japan FCS*				
2013	Australia				
2015	EU Annex I Renewal (BFR)*				
2015	Canada PMRA Registration Rev.*				
2015	US EPA Registration Rev *				

	Tumors related to treatment?	MON Mouse	MON Rat 1	MON Rat 2	CHEM Mouse
2015	WHO/IARC	Yes	Yes	Yes	Yes
1987	WHO/JMPR	No	No		
1991	US EPA Cancer Classification	No	No	No	
1991	Canada PMRA	No	No	No	
1993	US EPA RED	No	No	No	
1994	WHO/IPCS	No	No	No	
1999	Japan FCS	No	No	No	
2000	FAO Specifications	No	No	No	
2002	EU Annex I	No	No	No	No
2004	WHO/JMPR	No	No	No	No
2005	WHO/Water Sanitation Health	No	No	No	
2007	OEHHA	No	No	No	No
2007	Brazil Anvisa*	No	No	No	No
2008	US EPA Effects Determination	No		No	
2010	Japan FCS*	No	No	No	
2013	Australia	No	No	No	No
2015	EU Annex I Renewal (BFR)*	No	No	No	No
2015	Canada PMRA Registration Rev.*	No	No	No	No
2015	US EPA Registration Rev *	No	No	No	No

	Tumors related to treatment?	MON Mouse	MON Rat 1	MON Rat 2	CHEM Mouse	Additional Carc Studies
2015	WHO/IARC	Yes	Yes	Yes	Yes	
1987	WHO/JMPR	No	No			
1991	US EPA Cancer Classification	No	No	No		
1991	Canada PMRA	No	No	No		
1993	US EPA RED	No	No	No		
1994	WHO/ IPCS	No	No	No		
1999	Japan FCS					
2000	FAO Specifi					
2002	EU Annex I				No	2R
2004	WHO/JMPR				No	2R
2005	WHO/ Wate					
2007	OEHHA	No	No	No	No	
2007	Brazil Anvisa*	No	No	No		?R/?M
2008	US EPA Effects Determination	No		No		
2010	Japan FCS*	No	No	No		3R/3M
2013	Australia	No	No	No	No	
2015	EU Annex I Renewal (BFR)*	No	No	No	No	7R/3M
2015	Canada PMRA Registration Rev.*	No	No	No	No	2R
2015	US EPA Registration Rev.*	-	-	-	-	?R/?M

"Based on the weight of evidence, glyphosate is judged unlikely to pose a cancer hazard to humans."





Evaluation of the NSRL for Glyphosate

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Initial Assumptions in Estimating a NSRL for Glyphosate

Glyphosate is listed

Glyphosate causes the tumor types identified in the IARC classification

The pool of studies is not limited to the studies considered by IARC

Studies must meet generally accepted principles and be "of sufficient quality"

Linear multistage model is appropriate

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Basis for Proposed Labor Code Listing of Glyphosate

NSRL must be "based on evidence and standards of comparable scientific validity to the evidence and standards which for the scientific basis for the listing of such chemical pursuant to subdivision (a) of Section 25249.8."

Basis for listing is the IARC classification:

- Group 2A
- Sufficient evidence in animals

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IARC Evaluation of Mouse Studies

Positive trend in hemangiosarcoma in male CD-1 mice in one study (Cheminova, 1993)

Positive trend in renal tubule carcinoma (alone or combined with adenoma) in male CD-1 mice in one study (Monsanto, 1983)

IARC evaluated only 2 of the 5 long-term carcinogenicity studies of glyphosate in mice

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IARC Disregarded Most Carcinogenicity Studies of Glyphosate

Long-term Carcinogenicity Studies in:	No. of Publicly Available Studies	No. of Studies Relied on by IARC
Mice	5	2
Rats	9	2

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Hemangiosarcoma Data from 5 Studies of Glyphosate in Male Mice

Dose mg/kg-d	0	14.5	85	100	150	157	165	267	300	814	838	946	1000	1454	4348	4841
Study 1	0/50			0/50					0/50				4/50			
Study 2	0/49					0/50				0/50						0/50
Study 3	0/50						0/50				0/50				2/50	
Study 4	2/51		1/51					2/51				1/51				
Study 5	0/22	0/20			1/22									0/27		

Study 1: Cheminova (1993)
Study 2: Monsanto (1983)
Study 3: Arysta Life (1997)
Study 4: Nufarm (2009)
Study 5: Feinchemie (2001)

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BMD Modeling of Hemangiosarcoma Tumor Data in Male Mice

Approach	BMD_{10} mg/kg-d	$BMDL_{10}$ mg/kg-d	Model fits the data?
All five studies (pooled); all models	--	--	No
All five studies (excl. doses >1000 mg/kg-d) LMS	1630	1230	Yes
Studies 1 and 2 only (pooled); all models	--	--	No
Study 1 only; LMS model	1080	822	Yes
Study 3 only; LMS model	7120	4370	Yes
Studies 1 & 3 only (pooled); LMS model	5814	3178	No ($p = 0.07$)

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Renal Tubule Tumor Data from 5 Studies of Glyphosate in Male Mice

Dose mg/kg-d	0	14.5	85	100	150	157	165	267	300	814	838	946	1000	1454	4348	4841
Study 1	2/50			2/50					0/50				0/50			
Study 2	1/49					0/50				1/50						3/50
Study 3	0/50						0/50				0/50				2/50	
Study 4	0/51		0/51					0/51				0/51				
Study 5	0/22	0/20			0/22									2/27		

Study 1: Cheminova (1993)
Study 2: Monsanto (1983)
Study 3: Arysta Life (1997)
Study 4: Nufarm (2009)
Study 5: Feinchemie (2001)

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BMD Modeling of Kidney Tumor Data in Male Mice

Approach	BMD_{10} mg/kg-d	$BMDL_{10}$ mg/kg-d	Model fits the data?
All five studies (pooled); LMS model	6990	4820	Yes
Studies 1 & 2 (pooled); LMS model	6480	4600	Yes
Study 2 only; LMS model	7750	4110	Yes

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IARC Evaluation of Rat Studies

Significant increase (but no positive trend and no apparent progression to carcinoma) in pancreatic islet cell adenomas in male SD rats in two studies (Monsanto, 1981, 1990)

IARC relied on only 2 of the 9 long-term carcinogenicity studies of glyphosate in rats

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Pancreatic Islet Cell Tumor Data from 7 Studies of Glyphosate in Male Rats

Dose	0	3	7.4	10	31	74	86	89	100	104	121	285	300	354	361	362	741	940	1000	1077	1127	1214
S.1	0/50	5*/49		2/50	3/50																	
S.2	2/58							8*/57								5/60		7/59				
S. 3	1/64										2/64				0/64							1/64
S. 4	7/50			1/24					2/17				2/21						1/49			
S. 5	4/76									1/75				2/80							1/78	
S. 6	4/51						1/51					2/51								1/51		
S. 7	3/48		0/30			0/32											1/49					

Study 1: Monsanto (1981) S.D. rats
Study 2: Monsanto (1990) S.D. rats
Study 3: Syngenta (2001) S.D. rats
Study 4: Cheminova (1993) S.D. rats

Study 5: Arysta Life (1997) S.D. rats
Study 6: Nufarm (2009) Wistar rats
Study 7: Feinchemie (1996) Wistar rats

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BMD Modeling of Pancreatic Islet Tumor Data in Male Rats

Approach	BMD_{10} mg/kg-d	$BMDL_{10}$ mg/kg-d	Model fits the data?
All 5 studies in SD rats (pooled); all models	--	--	No
All 5 studies in SD rats (excl >940 mg/kg-d); all models	--	--	No
Study 2 only; LMS model	2070	634	Yes
Studies 1 & 2 only; all models	--	--	No

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Evaluation of NSRL

Tumor	Approach	$BMDL_{10}$ mg/kg-d	Estimated NSRL mcg/day
Hemangiosarcoma in male mice	All five studies (pooled); no models fit the data	--	--
Kidney tumors in male mice	All five studies (pooled); LMS	4820	4820
Pancreatic tumors in male rats	All five studies (pooled); no models fit the data	--	--

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Thank You