Appointment

From: Bolen, Derrick [/o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1ffc58b0468c4deca51a8bad735b7d95-Bolen, Derr]
Sent: 11/2/2017 7:44:39 PM
To: Beck, Nancy [Beck.Nancy@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Erik Baptist (baptist.erik@epa.gov) [baptist.erik@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]; Epp, Timothy [Epp.Timothy@epa.gov]
CC: Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Strauss, Linda [Strauss.Linda@epa.gov]; Reighart, Andrew [Reighart.Andrew@epa.gov]; Yarger, Ryne [Yarger.Ryne@epa.gov]; Messina, Edward [Messina.Edward@epa.gov]; Anderson, Neil [Anderson.Neil@epa.gov]

Subject: WPS & C&T Meeting
Attachments: WPS & C&T Meeting ; Untitled Attachment; WPS & C&T Meeting ; WPS & C&T Meeting ; Untitled Attachment; Untitled Attachment; Untitled Attachment; WPS & C&T Meeting ; WPS & C&T Meeting ; WPS & C&T Meeting Options Selection pre-brief; Untitled Attachment; WPS & C&T Meeting ; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment; Untitled Attachment
Location: PY-S4621; (Call in number Conference Line/Code / Ex. 6

Start: 11/21/2017 9:00:00 PM
End: 11/21/2017 9:30:00 PM
Show Time As: Busy

Recurrence: Weekly
every Tuesday from 4:00 PM to 4:30 PM

Appointment

To: Beck, Nancy [beck.nancy@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Michael Dourson (dourson.michael@epa.gov) [dourson.michael@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mclean, Kevin [Mclean.Kevin@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]

CC: Baptist, Erik [baptist.erik@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Burke, Marcella [burke.marcella@epa.gov]

Subject: WPS & C&T Meeting

Attachments: Cert rule FR Notice on changes coming 12 04 17.docx; WPS FR Notice on changes coming 12 04 17.docx

Start: 12/5/2017 9:00:00 PM

End: 12/5/2017 9:30:00 PM

Show Time As: Busy

Recurrence: (none)

Appointment

To: Beck, Nancy [beck.nancy@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Michael Dourson (dourson.michael@epa.gov) [dourson.michael@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]

CC: Baptist, Erik [baptist.erik@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]

Attachments: Summary - Key Aspects WP & CT.DOCX; WPS and Certification Rule Weekly Meeting #3 Nov 21 2017.docx; Worker list of training topics DAA fact sheet.docx; Minimum Age Background Information v2.docx; Certification Timeline 11 15 17.pdf

Start: 11/21/2017 9:00:00 PM
End: 11/21/2017 9:30:00 PM

Recurrence: (none)

Appointment

To: Beck, Nancy [beck.nancy@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Michael Dourson (dourson.michael@epa.gov) [dourson.michael@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Lee, Andrew [lee.andrew@epa.gov]; Michael Dourson (dourson.michael@epa.gov) [dourson.michael@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; bolen.derrick@epa.gov

CC: Baptist, Erik [baptist.erik@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]

Subject: WPS & C&T Meeting

Attachments: WPS and Certification Rule Weekly Meeting #4 Nov 28 2017.docx; Minimum Age Background Information 11 27 17.docx; AEZ Issue Paper 11 27 17.docx

Start: 11/28/2017 9:00:00 PM

End: 11/28/2017 9:30:00 PM

Recurrence: (none)

Appointment

To: Beck, Nancy [beck.nancy@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Michael Dourson (dourson.michael@epa.gov) [dourson.michael@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]

CC: Baptist, Erik [baptist.erik@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Burke, Marcella [burke.marcella@epa.gov]

BCC: DCRoomEast3156/DC-EPA-EAST-OCSPP [DCRoomEast3156@epa.gov]

Subject: WPS & C&T Meeting

Attachments: WPS and CT NPRM Schedule 12 04 17 (002).docx

Location: DCRoomEast3156/DC-EPA-EAST-OCSPP (Call in number: **Conference Line/Code / Ex. 6**

Start: 12/13/2017 2:30:00 PM

End: 12/13/2017 3:00:00 PM

Show Time As: Busy

Recurrence: (none)

Appointment

To: Beck, Nancy [beck.nancy@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Michael Dourson (dourson.michael@epa.gov) [dourson.michael@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]

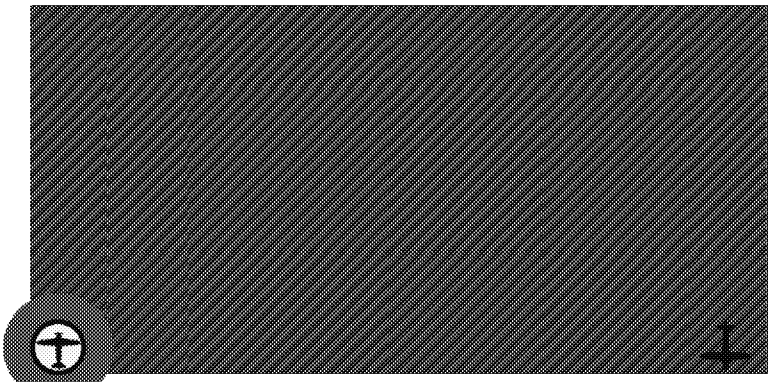
CC: Baptist, Erik [baptist.erik@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Burke, Marcella [burke.marcella@epa.gov]

Attachments: WPS and Certification Rule Weekly Meeting Dec 20 2017.docx; DRAFT AEZ HTC Fact Sheet 12-20-17 .docx; AEZ animation - general.pptx; AEZ animation - people in AEZ off establishment.pptx

Start: 12/21/2017 9:00:00 PM
End: 12/21/2017 9:30:00 PM
Show Time As: Busy

Recurrence: (none)

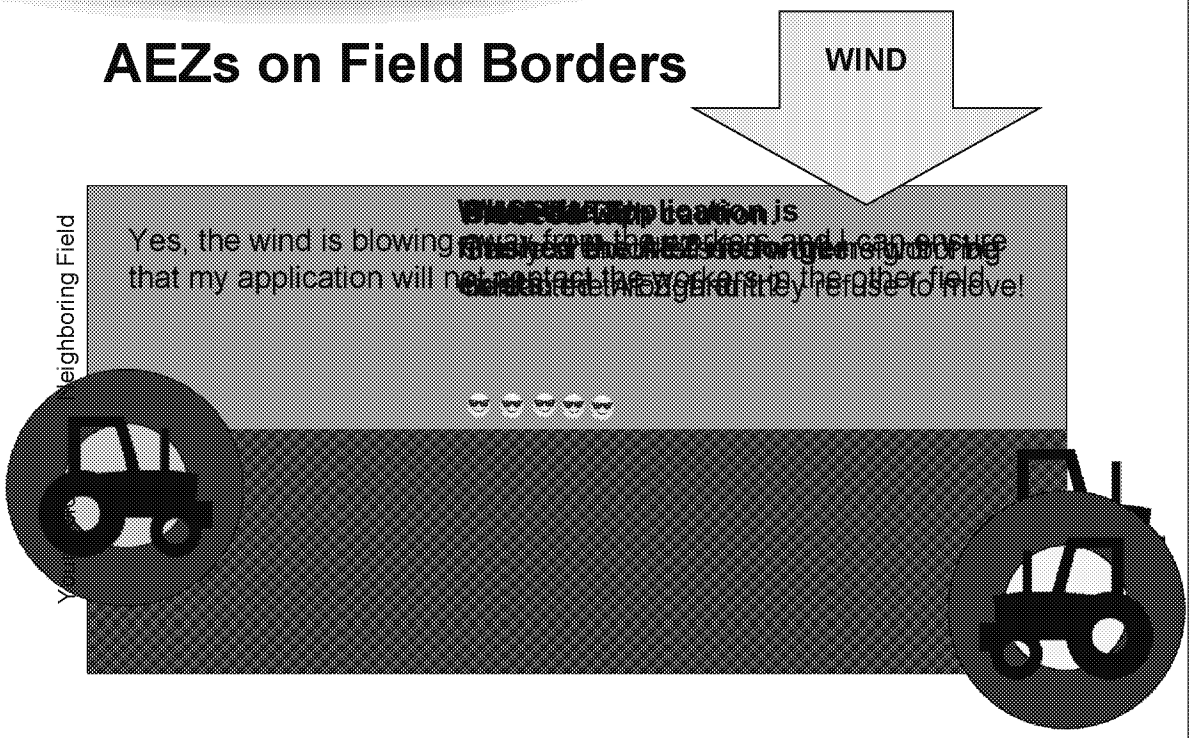
Application Exclusion Zone in Outdoor Production



When the application is concluded, the AEZ no longer exists.

Field | AEZ | Spray Area | Treated Area (REI Area)

AEZs on Field Borders



Appointment

To: Beck, Nancy [beck.nancy@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Michael Dourson (dourson.michael@epa.gov) [dourson.michael@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; bolen.derrick@epa.gov; Lee, Andrew [lee.andrew@epa.gov]; Michael Dourson (dourson.michael@epa.gov) [dourson.michael@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]

CC: Baptist, Erik [baptist.erik@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Burke, Marcella [burke.marcella@epa.gov]

Start: 1/4/2018 6:00:00 PM
End: 1/4/2018 6:30:00 PM
Show Time As: Busy

Recurrence: (none)

Appointment

To: Beck, Nancy [beck.nancy@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Michael Dourson (dourson.michael@epa.gov) [dourson.michael@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]

CC: Baptist, Erik [baptist.erik@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Burke, Marcella [burke.marcella@epa.gov]; Kaczmarek, Chris [Kaczmarek.Chris@epa.gov]

Attachments: WPS and Certification Rule Weekly Meeting - 1-10-18.docx

Location: DCRoomEast3156/DC-EPA-EAST-OCSPP (Call in **Conference Line/Code / Ex. 6**

Start: 1/10/2018 9:00:00 PM

End: 1/10/2018 9:30:00 PM

Show Time As: Busy

Recurrence: (none)

Appointment

To: Beck, Nancy [beck.nancy@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]

CC: Baptist, Erik [baptist.erik@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Burke, Marcella [burke.marcella@epa.gov]; Strauss, Linda [Strauss.Linda@epa.gov]

BCC: DCRoomEast3156/DC-EPA-EAST-OCSPP [DCRoomEast3156@epa.gov]

Subject: WPS & C&T Meeting

Attachments: CLEAN DRAFT WPS Options Selection Draft 1.16.18.docx

Location: DCRoomEast3156/DC-EPA-EAST-OCSPP (Call in **Conference Line/Code / Ex. 6**

Start: 1/17/2018 7:00:00 PM

End: 1/17/2018 7:30:00 PM

Show Time As: Busy

Recurrence: (none)

Appointment

To: Beck, Nancy [beck.nancy@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mclean, Kevin [Mclean.Kevin@epa.gov]

CC: Baptist, Erik [baptist.erik@epa.gov]; Burke, Marcella [burke.marcella@epa.gov]; Strauss, Linda [Strauss.Linda@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Reighart, Andrew [Reighart.Andrew@epa.gov]

Subject: WPS & C&T Meeting

Start: 1/23/2018 7:45:00 PM
End: 1/23/2018 8:15:00 PM

Recurrence: (none)

Appointment

To: Beck, Nancy [beck.nancy@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; bolen.derrick@epa.gov; Lee, Andrew [lee.andrew@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]

CC: Baptist, Erik [baptist.erik@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Burke, Marcella [burke.marcella@epa.gov]; Strauss, Linda [Strauss.Linda@epa.gov]; Reighart, Andrew [Reighart.Andrew@epa.gov]; Maguire, Kelly [Maguire.Kelly@epa.gov]

Subject: WPS & C&T Meeting Options Selection pre-brief

Location: PY-S4621 (Call in number **Conference Line/Code / Ex. 6**

Start: 2/20/2018 9:15:00 PM

End: 2/20/2018 10:00:00 PM

Show Time As: Busy

Recurrence: (none)

Appointment

To: Beck, Nancy [beck.nancy@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]

CC: Baptist, Erik [baptist.erik@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Burke, Marcella [burke.marcella@epa.gov]; Strauss, Linda [Strauss.Linda@epa.gov]; Reighart, Andrew [Reighart.Andrew@epa.gov]

Start: 2/13/2018 9:15:00 PM
End: 2/13/2018 9:45:00 PM
Show Time As: Busy

Recurrence: (none)

Appointment

To: Beck, Nancy [beck.nancy@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mclean, Kevin [Mclean.Kevin@epa.gov]

CC: Baptist, Erik [baptist.erik@epa.gov]; Burke, Marcella [burke.marcella@epa.gov]; Strauss, Linda [Strauss.Linda@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Reighart, Andrew [Reighart.Andrew@epa.gov]

Subject: WPS & C&T Meeting

Location: PY-S4621; (Call in number Conference Line/Code / Ex. 6

Start: 3/6/2018 9:00:00 PM

End: 3/6/2018 9:30:00 PM

Recurrence: (none)

365 Call-in number issues Please use the conference line listed above. Thanks.

Appointment

To: Beck, Nancy [beck.nancy@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mclean, Kevin [Mclean.Kevin@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; bolen.derrick@epa.gov

CC: Baptist, Erik [baptist.erik@epa.gov]; Burke, Marcella [burke.marcella@epa.gov]; Strauss, Linda [Strauss.Linda@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Reighart, Andrew [Reighart.Andrew@epa.gov]

Start: 3/13/2018 8:00:00 PM
End: 3/13/2018 8:30:00 PM

Recurrence: (none)

Appointment

To: Beck, Nancy [Beck.Nancy@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]; Baptist, Erik [baptist.erik@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mclean, Kevin [Mclean.Kevin@epa.gov]; Epp, Timothy [Epp.Timothy@epa.gov]

CC: Strauss, Linda [Strauss.Linda@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Reighart, Andrew [Reighart.Andrew@epa.gov]; Yarger, Ryne [Yarger.Ryne@epa.gov]; Messina, Edward [Messina.Edward@epa.gov]; Anderson, Neil [Anderson.Neil@epa.gov]

Start: 8/14/2018 8:00:00 PM
End: 8/14/2018 8:30:00 PM

Recurrence: (none)

Appointment

To: Beck, Nancy [beck.nancy@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]

CC: Baptist, Erik [baptist.erik@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Strauss, Linda [Strauss.Linda@epa.gov]; Reighart, Andrew [Reighart.Andrew@epa.gov]; Yarger, Ryne [Yarger.Ryne@epa.gov]; Burke, Marcella [burke.marcella@epa.gov]

Location: DCRoomEast3156/DC-EPA-EAST-OCSPP (Call in Number **Conference Line/Code / Ex. 6**

Start: 4/12/2018 2:30:00 PM
End: 4/12/2018 3:00:00 PM
Show Time As: Busy

Recurrence: (none)

Appointment

To: Beck, Nancy [beck.nancy@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mclean, Kevin [Mclean.Kevin@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; bolen.derrick@epa.gov

CC: Baptist, Erik [baptist.erik@epa.gov]; Strauss, Linda [Strauss.Linda@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Reighart, Andrew [Reighart.Andrew@epa.gov]; Yarger, Ryne [Yarger.Ryne@epa.gov]; Messina, Edward [Messina.Edward@epa.gov]

Start: 4/17/2018 8:00:00 PM
End: 4/17/2018 8:30:00 PM

Recurrence: (none)

Appointment

To: Hofmann, Angela [Hofmann.Angela@epa.gov]; Mosby, Jackie [Mosby.Jackie@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Beck, Nancy [Beck.Nancy@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Bolen, Derrick [bolen.derrick@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Miller, Wynne [Miller.Wynne@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Keigwin, Richard [Keigwin.Richard@epa.gov]; Bolen, Brittany [bolen.brittany@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]

CC: Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Anderson, Neil [Anderson.Neil@epa.gov]; Baptist, Erik [baptist.erik@epa.gov]; Yarger, Ryne [Yarger.Ryne@epa.gov]; Messina, Edward [Messina.Edward@epa.gov]; Reighart, Andrew [Reighart.Andrew@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Strauss, Linda [Strauss.Linda@epa.gov]

BCC: DCRoomEast3156/DC-EPA-EAST-OCSPP [DCRoomEast3156@epa.gov]

Location: DCRoomEast3156/DC-EPA-EAST-OCSPP (Call in Number **Conference Line/Code / Ex. 6**

Start: 5/17/2018 7:00:00 PM
End: 5/17/2018 7:30:00 PM
Show Time As: Busy

Recurrence: (none)

Appointment

To: Beck, Nancy [Beck.Nancy@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]; Baptist, Erik [baptist.erik@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; bolen.derrick@epa.gov; Lee, Andrew [lee.andrew@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]

CC: Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Strauss, Linda [Strauss.Linda@epa.gov]; Reighart, Andrew [Reighart.Andrew@epa.gov]; Yarger, Ryne [Yarger.Ryne@epa.gov]; Messina, Edward [Messina.Edward@epa.gov]; Anderson, Neil [Anderson.Neil@epa.gov]

Location: DCRoomEast3156/DC-EPA-EAST-OCSPP (Call in Number **Conference Line/Code / Ex. 6**

Start: 5/24/2018 3:00:00 PM
End: 5/24/2018 3:30:00 PM
Show Time As: Busy

Recurrence: (none)

Appointment

To: Beck, Nancy [Beck.Nancy@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Erik Baptist (baptist.erik@epa.gov) [baptist.erik@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Jeffrey Sands (sands.jeffrey@epa.gov) [sands.jeffrey@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]

CC: Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Strauss, Linda [Strauss.Linda@epa.gov]; Reighart, Andrew [Reighart.Andrew@epa.gov]; Yarger, Ryne [Yarger.Ryne@epa.gov]; Messina, Edward [Messina.Edward@epa.gov]; Anderson, Neil [Anderson.Neil@epa.gov]

Location: DCRoomEast3156/DC-EPA-EAST-OCSPP (Call in Number **Conference Line/Code / Ex. 6**

Start: 5/29/2018 6:30:00 PM
End: 5/29/2018 7:00:00 PM
Show Time As: Busy

Recurrence: (none)

Appointment

To: Beck, Nancy [Beck.Nancy@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Erik Baptist (baptist.erik@epa.gov) [baptist.erik@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]; Epp, Timothy [Epp.Timothy@epa.gov]

CC: Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Strauss, Linda [Strauss.Linda@epa.gov]; Reighart, Andrew [Reighart.Andrew@epa.gov]; Yarger, Ryne [Yarger.Ryne@epa.gov]; Messina, Edward [Messina.Edward@epa.gov]; Anderson, Neil [Anderson.Neil@epa.gov]

Location: DCRoomEast3156/DC-EPA-EAST-OCSPP (Call in Number **Conference Line/Code / Ex. 6**

Start: 6/5/2018 8:00:00 PM
End: 6/5/2018 8:30:00 PM
Show Time As: Busy

Recurrence: (none)

Appointment

To: Beck, Nancy [Beck.Nancy@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Fitz, Nancy [Fitz.Nancy@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Richard Keigwin [Keigwin.Richard@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Wynne Miller [Miller.Wynne@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Berwald, Derek [Berwald.Derek@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Parrott, Patricia [parrott.patricia@epa.gov]; Arling, Michelle [Arling.Michelle@epa.gov]; Dinkins, Darlene [Dinkins.Darlene@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; bolen.derrick@epa.gov; Mosby, Jackie [Mosby.Jackie@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Smith, Peterj [Smith.Peterj@epa.gov]; Hofmann, Angela [Hofmann.Angela@epa.gov]; Mclean, Kevin [Mclean.Kevin@epa.gov]; Erik Baptist (baptist.erik@epa.gov) [baptist.erik@epa.gov]; Lee, Andrew [lee.andrew@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Peffers, Mel [Peffers.Mel@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]; Epp, Timothy [Epp.Timothy@epa.gov]

CC: Wise, Louise [Wise.Louise@epa.gov]; Hoyt, Sarita [Hoyt.Sarita@epa.gov]; Nelson, Tomeka [Nelson.Tomeka@epa.gov]; Strauss, Linda [Strauss.Linda@epa.gov]; Reighart, Andrew [Reighart.Andrew@epa.gov]; Yarger, Ryne [Yarger.Ryne@epa.gov]; Messina, Edward [Messina.Edward@epa.gov]; Anderson, Neil [Anderson.Neil@epa.gov]; Burke, Marcella [burke.marcella@epa.gov]

Location: DCRoomEast3156/DC-EPA-EAST-OCSPP (Call in Number Conference Line/Code / Ex. 6)

Start: 6/12/2018 8:00:00 PM
End: 6/12/2018 8:30:00 PM
Show Time As: Busy

Recurrence: (none)

Message

From: Keller, Kaitlin [keller.kaitlin@epa.gov]
Sent: 6/7/2018 8:48:09 PM
To: Beck, Nancy [Beck.Nancy@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Baptist, Erik [Baptist.Erik@epa.gov]; Keigwin, Richard [Keigwin.Richard@epa.gov]
Subject: WPS interpretative policy
Attachments: wps_interpretive_policy_06_26_15.pdf

Attached. There may be other documents that the team can provide, but this is the one I found that specifically discusses the issue.

From the attached:

7-4 Small establishments, applicability of WPS

Question: Are small agricultural establishments exempted from compliance with the Worker Protection Standard?

Answer: No. Except for a partial exemption for owners and their immediate families (immediate family includes only spouse, children, stepchildren, foster children, parents, stepparents, foster parents, brothers, and sisters), all agricultural establishments that use pesticides that have WPS labeling must comply with the Standard when using those products for uses within the scope of the WPS. (March 22, 1993)

14-24 Production of agricultural plants for other than direct sale
Question: What is the scope of the WPS with respect to establishments producing agricultural plants for other than direct sale, i.e., in-house use?

Answer: There is no exception for agricultural plants produced for other than direct sale, i.e., in-house use. The WPS covers an agricultural establishment if (1) a WPS-labeled agricultural pesticide is used on the establishment, (2) workers or handlers are employed by or on the agricultural establishment, (3) the establishment is a farm, forest, nursery, or greenhouse, as defined in the WPS, and (4) the establishment or the activity is not covered by one of the exceptions specifically described in the rule, Section 170.102 (b). For instance, the following operations are covered by the WPS: Production of hay or feed grown for livestock on dairy farms, cattle ranches, or other livestock operations; sod farms, greenhouses, or nurseries operated by golf courses; and greenhouses and nurseries operated by theme parks, hotel chains, botanical gardens, and state and local governments. (Note: Pasture and rangeland used for grazing are excluded.) (March 15, 1995)

Kaitlin Keller, Special Assistant
Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency
(202) 564-7098

Agricultural Worker Protection Standard 40 CFR Parts 156 & 170 Interpretive Policy

Document Contents

1 Accelerated Provisions
2 Crop Advisors
3 Decontamination
4 Definitions
5 Entry Restrictions
6 Equivalency Issues
7 Exemptions and Exceptions
8 Generic Requirements
9 Handler Activities
10 Labeling Issues
11 Notice of Application
12 Personal Protective Equipment (PPE)
13 Posting Signs/Display of Information
14 Scope
15 Training
16 Enforcement and Liability
17 Activities Covered by the WPS

1 Accelerated Provisions

1-1 Ventilation criteria

Question: The accelerated provisions do not reference section 170.110(c)(3) (established ventilation criteria) as cited in section 170.112(b)(2) and (c)(3). Therefore, it appears that the ventilation criteria provisions are not part of the accelerated implementation. Other requirements do make applicable references.

Answer: Any ventilation requirement specified on product labeling must be met. The ventilation criteria in the WPS are not part of the accelerated provisions. (March 22, 1993)

1-2 Labeling in reference to...

Question: How can EPA require compliance with the accelerated provisions if they are not on the label? The mechanism of the entire worker protection changes were intended to be done via the label (i.e., label statements and reference to part 170.)

Answer: The WPS reference must be on the label before the accelerated provisions are applicable. (March 22, 1993)

2 Crop Advisors

2-1 Status under the WPS

Question: Which training standards apply to the crop advisor? If the advisor is defined as a handler, does this mean that more than 1 hour per 24 hours can be spent doing pest assessments in treated fields? If not, is the time limited to one hour per field or to all treated areas in a 24 hour period? If crop advisors are limited to short-term activities, the impact has potential adverse impacts affecting integrated pest management systems, pest insurgence, pesticide use, and valuable services available to production agriculture.

ED_001854_00008312-00001

Answer: If crop advisors enter an area during an application or an REI they are considered handlers and must be trained as handlers. This allows the crop advisor unlimited access to the field during the REI, provided he/she is provided all other WPS handler protections. If advisors are employees of the agricultural establishment and enter field after the REI is over, they are considered workers and would receive worker training if not already trained as a handler. If they are not employed by the agricultural establishment (i.e., for-hire) they are not protected by the WPS after the termination of the REI. NOTE: Crop advisors will be addressed in the How-To-Comply Manual. (March 22, 1993)

2-2 Knowledge of site-specific information

Question: When must crop advisors employed by a commercial pesticide handling establishment be informed of pesticide treatments or treated areas?

Answer: At 40 CFR part 170.232(b), the WPS requires that whenever a handler, (e.g., a crop advisor), who is employed by a commercial pesticide handling establishment will be performing handling tasks, (i.e., scouting), on an agricultural establishment, the handler employer must assure that the handler is aware of the following information concerning any areas on the agricultural establishment that the handler may be in (or walk within 1/4 mile of) and that may be treated with a pesticide or that may be under a restricted-entry interval while the handler will be on the agricultural establishment:

(1) Specific location and description of any such areas; and
(2) Restrictions on entering those areas.

For example, if commercial crop advisors are scheduled to scout in an area on a farm that remains under an REI, they need to be told the specific location and description of the area and what personal protective equipment they must wear while in that area.

NOTE: The agricultural employer is required to make sure that commercial handler employers have this information. (40 CFR part 170.124)

If crop advisors will be in or on a *vehicle within 1/4 mile* of the treated area, but not in the treated area, no notification is necessary.

If crop advisors are in or on a vehicle in the treated area, notification is necessary.

If crop advisors are on foot, they must be notified if they are in the treated or within 1/4 mile of the treated area.

NOTE: For more information on crop advisors, see the How To Comply Manual, What Employees Need To Know. (February 24, 1994)

3 Decontamination

3-1 Size of eyeflush containers

Question: Does the eyeflush water requirement of Section 170.150 need to be in one pint containers only? Can a single, large container suffice if the contents equal or exceed one pint per worker?

Answer: A single large container would suffice if it were immediately accessible to each worker or handler who requires it. (March 22, 1993)

ED_001854_00008312-00002

3-2 Single-use towels

Question: Section 170.150(c)(i) requires "single-use towels" at the decontamination site for workers. However, if early entry activities are performed, "clean towels" are allowed. Why the difference?

Answer: There are two separate requirements for decontamination sites for early-entry workers (and there are two for handlers):

(1) While they are performing early-entry tasks, early-entry workers must be provided a decontamination site that includes single-use towels.

(2) In addition, at the end of their exposure period, early-entry workers must be provided a decontamination site at the place where they remove their personal protective equipment. At this site, "clean towels" (single-use or reusable cloth) are allowed, because this site could be equipped with a shower and single-use towels would be awkward for whole-body drying. (March 22, 1993)

3-3 Decontamination materials for flaggers

Question: Section 170.250 specifies the decontamination requirements for handling activities. Must the employer handler provide separate decontamination materials for flaggers?

Answer: Decontamination facilities for flaggers must be within 1/4 mile of the flagger. If the decontamination site for handlers (i.e., aerial applicators) is more than 1/4 mile from each flagger, then there must be a separate decontamination site to serve such flaggers. For tasks performed more than 1/4 mile from the nearest point reachable by vehicles (cars, trucks, or tractors), the decontamination site may be at the access point. In this circumstance, clean water from springs, streams, lakes, or other sources may be used for decontamination, if such water is more readily available that the water at the decontamination site. (March 22, 1993)

3-4 Immediate availability of eyeflush

Question: In 40 CFR part 170.150(b)(4), the WPS requires the agricultural employer to assure that at least 1 pint of water is immediately available to each worker performing early-entry activities and for which the pesticide labeling requires protective eyewear.

Similarly, 40 CFR part 170.250(d), requires the handler employer to assure that at least 1 pint of water is immediately available to each handler who is performing tasks for which the pesticide labeling requires protective eyewear.

What is meant by "immediately available"?

Answer: In both sections of the WPS addressing availability of eyeflush water, the Agency requires that emergency eyeflush water be carried by the handler or early-entry worker, or be on the vehicle (or aircraft) which the handler or early-entry worker is using, or be otherwise immediately accessible. (40 CFR parts 170.150(b)(4) and 170.250(d))

The How-to-Comply with the Worker Protection Standard Manual states that emergency eyeflush water may be at the decontamination site if the decontamination site is immediately accessible.

ED_001854_00008312-00003

Because the WPS specifies that eyewash water must be carried by the handler or early-entry worker, or must be on the vehicle or aircraft that the handler or early-entry worker is using, the eyewash water must be close and accessible to the worker or handler at all times. In addition, because concentrations and causticity of agricultural chemicals vary so greatly (and therefore the duration of exposure necessary for ocular damage to occur is difficult to uniformly determine), emergency eyewash water must be available immediately. If the emergency eyewash water is not being carried on one's person, it must be situated at such a distance that one could get to it within very few seconds. (November 17, 1993)

3-5 Examples of immediate availability

Question: If emergency eyeflush water must be close, accessible, and situated so that one could get to it within very few seconds, what are some examples of places that it may be located/stored so that the above criteria are met?

Answer: In addition to the examples listed above, the following might be additional examples of "immediately available":

(1) Running water, a commercial eyeflush dispenser, or decontamination water in a carboy at a mix/load, storage, equipment cleaning or repairing, or other stationary handling (or early-entry) site for handlers or early entry workers engaged in such activities at the site.

(2) Running water or commercial eyeflush dispensers that are located at frequent intervals and are easily accessed by the handlers/early-entry workers in a bench-type nursery or greenhouse site.

(3) Water that meets the WPS standard for decontamination water that is in a nurse tank or other supply tank that is on (or being dragged by) the vehicle a handler or early-entry worker is operating. (November 17, 1993)

3-6 Examples of unacceptable locations for eyeflush

Question: What are some examples of *unacceptable* locations in which to store emergency eyeflush water (i.e., water would NOT be immediately available)?

Answer: Examples of situations where emergency eyeflush water would NOT be immediately accessible are:

(1) Water on a vehicle but in a locked compartment.

(2) Water for which difficult or time-consuming steps must be taken to access, such as having to uncouple or connect a nurse tank hose, having to unlock a compartment holding the eyeflush dispenser or having to unlock a restroom.

(3) Water located across a stream or commercial road. (November 17, 1993)

3-7 WPS and OSHA requirements for decontamination water

Question: Does the WPS requirement for the use of water safe for drinking preempt OSHA requirements for potable water in its Field Sanitation Standard if the business is currently subject to OSHA standards?

ED_001854_00008312-00004

Answer: No, the WPS requirement does not preempt the OSHA requirement for potable water. Please note that the EPA requirement is not for "water safe for drinking" but that the water be of such a quality and temperature that will not cause illness or injury when it contacts the skin or eyes or if it is swallowed.

OSHA's Field Sanitation Standard requires that potable drinking water be made available to workers. The water must be suitably cool and provided in sufficient amounts to meet the needs of all employees. By providing potable water which meets OSHA standards, an agricultural employer may meet the WPS water quality requirement. (March 7, 1995)

3-8 Decontamination requirements and handlers

Question: Does the EPA requirement for decontamination water cover handlers?

Answer: Yes. (See section 170.250.) (March 7, 1995)

3-9 Eyeflush water preemption

Question: Does the EPA's requirement for "eyeflush water" preempt other regulatory requirements for "eyeflush dispensers" for handlers and workers?

Answer: No, the EPA requirement does not preempt other requirements. It is acceptable to use eye flush dispensers provided all the WPS emergency eye flushing requirements are met. (March 7, 1995)

3-10 Decontamination facilities for consultants

Question: If the grower already has a decontamination facility, is that acceptable for a consultant going into the field since the handler-employer would not actually be "providing" it?

Answer: Yes, the handler employer could be providing the decontamination site if the employee has access to the grower's decontamination facility. The decontamination site must meet the WPS requirements.

In this situation, it is suggested that the handler employer work this out in advance with the grower. (March 7, 1995)

3-11 Use of diluent water for decontamination

Question: The regulation at 40 CFR part 170.150(b)(2) prohibits the use of water stored in a tank used for mixing pesticides for decontamination or eye flushing unless the tank is equipped with properly functioning valves or other mechanisms that prevent movement of the pesticides into the tank. From an enforcement standpoint, what are the "other mechanisms" that can be used to prevent movement of pesticides into the tank as discussed in Section 170.150(b)(2)? Would they include merely leaving an air gap between the water hose and the upper level of the pesticide mix in the spray tank?

Answer: Any device or mechanism that prevents contamination from the pesticide mix tank from entering the water tank is sufficient. Some examples include anti-back siphon devices, one-way or check valves, or an air gap sufficient to prevent contamination. (March 7, 1995)

ED_001854_00008312-00005

4 Definitions

4-1 Interpretation of the term "use"

Question: Section 170.9 states EPA's interpretation of the term "use." What regulatory effect does this interpretation have? Does this interpretation have the same effect as a definition? Why is it not included with the rest of the definitions in Part 170 rather than under the violations section?

Answer: The purpose of section 170.9 is to explain how the misuse provisions of FIFRA apply to the full range of pesticide-related activities addressed by the WPS. That need only be explained once while the terms in the definitions section are used repeatedly throughout the WPS. Therefore, listing definitions in one section is a convenience to readers. The discussion of "use" was included as opposed to a definition because the term "use" appears in the document in other contexts, e.g., use of PPE, use of equipment, plants used. (March 22, 1993)

4-2 When is a crop harvested?

Question: The WPS does not apply when any pesticide is applied to the harvested portions of agricultural plants or on harvested timber. (40 CFR parts 170.102(b)(9) and 170.202(b)(8)) For the purposes of the WPS, when is a crop harvested?

Answer: The WPS does not apply when any pesticide is applied to the harvested portions of agricultural plants or on harvested timber. Once a crop is harvested, workers performing activities related only to the harvested portion of the agricultural plant are not covered by the requirements of the WPS. NOTE: Harvesting includes packing produce into containers in the field.

For purposes of the WPS, an agricultural plant is considered harvested when:

(1) a desirable portion of the agricultural plant (seed, fruit, flower, stem, foliage, or roots) is detached from its parent, or

(2) a whole agricultural plant is separated from its growth media (soil, water, or other media).

Pesticide applications to harvested portions of agricultural plants or to harvested timber are not within the scope of the WPS.

Pesticide applications on an agricultural establishment that are within the scope of the WPS include:

(1) applications to the "parent" portion of the agricultural plant that remains after the crop has been harvested, if the application is made for the purposes of continuing the production of the "parent" plant or eliminating the "parent" plant.

(2) applications to the growth media that remains behind after the crop has been harvested, if the application is made for the purposes of (a) continuing the production of the "parent" plant or (b) eliminating the "parent" plant or (c) preparing the media for replanting or reseeding of an agricultural plant.

(3) applications to agricultural plants (including transplants) that are in growth media.

(4) applications to agricultural plants or plant portions (seeds, roots, bulbs, cuttings, etc) on an agricultural establishment immediately prior to or during planting, transplanting, or grafting.

ED_001854_00008312-00006

Note: This interpretation, for the purposes of the WPS, of when a crop is harvested is NOT intended to intrude on interpretations relating to "Days to Harvest" statements on pesticide labels. (November 17, 1993)

4-3(a) Sod/turf growing establishments, nursery

Question: Under what circumstances is an agricultural establishment growing sod/turf considered a nursery?

Answer: The WPS defines a nursery as any operation engaged in the outdoor production of any agricultural plant to produce cut flowers and ferns or plants that will be used in their entirety in another location. The definition states that such plants include turfgrass produced for sod.

As defined in 40 CFR part 170.3, sod/turf growing establishments are considered to be nurseries if the sod/turf is grown for commercial or research purposes and is to be used in its entirety in another location. (November 17, 1993)

4-3(b) Sod/turf growing establishments, farm

Question: Under what circumstances is an agricultural establishment growing sod/turf considered a farm?

Answer: The WPS defines a farm as any operation, other than a nursery or forest, engaged in the outdoor production of agricultural plants.

Agricultural establishments that are not nurseries and that are growing sod/turf outdoors for commercial or research purposes, for example, for seed production, are considered to be farms. (November 17, 1993)

4-4 Closed systems

Question: What is the definition of a closed system? What personal protective equipment is required when a closed system is used?

Answer: At 40 CFR part 170.240(d)(4), the WPS defines closed systems and allows exceptions to labeling required personal protective equipment (PPE) when a closed system is used provided certain conditions and requirements are met. These exceptions to PPE are allowed unless expressly prohibited by the product labeling.

Closed systems are systems designed by the manufacturer to enclose the pesticide to prevent it from contacting handlers or other people while it is being handled. Such systems must function properly and be used and maintained in accordance with the manufacturer's written operation instructions. Closed systems manufactured by a private person which meet the criteria in the regulations, including the requirement for written instructions, are acceptable.

Examples of closed systems include:

(1) closed mixing/loading systems.

(2) closed application systems designed to incorporate pesticides into soil, but only if the system does not allow any pesticide contact with the air throughout the entire application process.

(3) water soluble bags while the bag is intact.

The WPS provides that handler employers may allow handlers to omit some of the PPE listed on the pesticide labeling for a handling task if the handlers are using a closed system:

(1) When using a closed system to mix or load pesticides with the signal word "DANGER: or "WARNING," handlers need not wear all the PPE listed on the pesticide labeling, but must wear at least:

- long-sleeved shirt and long pants,
- shoes and socks,
- a chemical-resistant apron, and
- protective gloves specified on the pesticide labeling for mixing, loading, and other handling tasks.

2) When using a closed system to mix or load pesticides with the signal word "CAUTION," handlers need not wear all the PPE listed on the pesticide labeling, but must wear at least:

- long-sleeved shirt and long pants, and
- shoes and socks.

3) When using a closed system to do handling tasks other than mixing and loading with ANY pesticide, handlers need not wear all of the PPE listed on the pesticide labeling, but must wear at least:

- long-sleeved shirt and long pants, and
- shoes and socks.

4) When using a closed system that operates under pressure, handlers may wear the reduced PPE specified above, but must add protective eyewear.

Even when reduced PPE is permitted to be worn during a task, handlers must be provided all PPE required by the pesticide labeling for that task and have it immediately available for use in an emergency.

NOTE: For mixing/loading/transferring of pesticides outside the scope of WPS, follow the FIFRA Compliance Program Policy 12.2, Pesticides Closed Transfer, Mixing/Loading and Application Equipment (Closed Systems). (February 24, 1994)

4-5 Water-soluble bags

Question: Is a water soluble bag considered a closed system?

Answer: Yes, for WPS purposes, a water soluble bag is considered a closed loading system and, unless prohibited by the product labeling, handlers may be permitted to wear reduced personal protective equipment (PPE) as outlined in 40 CFR part 170.240(d)(4).

Once a water soluble bag is dissolved, broken, punctured, torn, or otherwise allows its contents to escape, it no longer a closed system and label specified PPE must be worn. In the case of routine mixing and loading with water soluble bags, label-specified PPE for the activity performed must be worn once the bags have lost their integrity, i.e., begin to dissolve in the tank, unless the mix tank and transfer system are closed systems. (February 24, 1994)

4-6(a) Enclosed cabs

ED_001854_00008312-00008

Question: What is the definition of an enclosed cab? What personal protective equipment is required when an enclosed cab is used?

Answer: At 40 CFR part 170.240(d)(5), the WPS defines enclosed cabs and allows exceptions to labeling required personal protective equipment (PPE) when handling tasks are performed from inside an enclosed cab provided certain conditions, including the type of cab, and requirements are met. These exceptions to PPE are allowed unless expressly prohibited by the product labeling.

Enclosed cabs must have a nonporous barrier that totally surrounds the occupants and prevents contact with pesticides outside of the cab.

Enclosed cabs that provide respiratory protection must have a properly functioning ventilation system that is used and maintained according to the manufacturer's written operating instructions. To substitute for a label-required respirator, the enclosed cab must be declared in writing by the manufacturer or by a governmental agency to provide at least as much respiratory protection as the type of respirator listed in the pesticide labeling.

Examples:

Some enclosed cab systems provide respiratory protection equivalent to a dust/mist filtering respirator and could, therefore, be used as a substitute when that type of respirator is specified in the product labeling.

Other enclosed cab systems are equipped to remove organic vapors as well as dusts and mists and could be used as a substitute when either the dust/mist filtering respirator or an organic vapor removing respirator is specified on the product labeling.

The WPS provides that handler employers may allow handlers to omit some of the PPE listed on the pesticide on the pesticide labeling for a handling task if the handlers are using an enclosed cab:

1) In enclosed cabs that do not provide respiratory protection handlers need not wear all PPE listed on the pesticide labeling, but must wear at least:

- long-sleeved shirt and long pants,
- shoes and socks,
- any respirator required for the handling task.

2) In enclosed cabs that provide respiratory protection equal to the labeling required respirator handlers need not wear all the PPE listed on the pesticide labeling but must wear at least:

- long-sleeved shirt and long pants, and
- shoes and socks.

3) In any enclosed cab where reduced PPE is worn, handlers must:

- keep immediately available all PPE listed on the labeling for the type of task being performed,
- wear the PPE if it is necessary to leave the cab and contact pesticide treated surfaces in the treated area,
- take off PPE that was worn in the treated are before entering the cab, and
- store all PPE in a chemical resistant container such as a plastic bag, to prevent contamination of the inside of the cab.

ED_001854_00008312-00009

NOTE: For pesticide applications utilizing an enclosed cab for uses outside the scope of WPS, follow the FIFRA compliance Program Policy 12.6, Enclosed Cab Use for Pesticide Applications. The Compliance Policy outlines slightly different conditions than the regulation. In addition, states may have additional requirements regarding the use of enclosed cabs. (February 24, 1994)

4-6(b) Open cabs

Question: Must an applicator, or other handler, performing handling tasks in a cab, i.e., tractor cab or truck cab, with the windows open wear all labeling prescribed PPE?

Answer: Yes, an applicator, or other handler, performing handling tasks in a cab, i.e., tractor or truck cab, with the windows open must wear all labeling prescribed PPE.

As discussed in the preceding question and answer, enclosed cabs must have a nonporous barrier that totally surrounds the occupants and prevents contact with pesticides outside of the cab. When the windows of the cab are open at any time during the handling activity, or the enclosure is otherwise breached, the cab is no longer considered enclosed and handlers would be required to wear the PPE required on the pesticide label for handlers of the product. (February 24, 1994)

4-7 When is a structure a greenhouse?

Question: If the sides of a greenhouse are constructed of porous cloth or other porous material is this structure considered a greenhouse?

Answer: No. The WPS definition of a greenhouse specifies that it is a structure enclosed with nonporous covering. Structures which are only enclosed with porous material such as cheesecloth or nylon screen are not considered greenhouses under the WPS. (February 28, 1995)

4-8 Is a structure a greenhouse; if windows and doors remain open during application

Question: If a greenhouse has windows or doors which remain open throughout an application, would this structure be considered a greenhouse?

Answer: Yes. Regardless of whether a greenhouse has windows or doors which are left open during the application, the structure is still a greenhouse and subject to the WPS provisions applicable to greenhouses. (February 28, 1995)

4-9 Is a structure a greenhouse; if walls are porous, or sides are removed

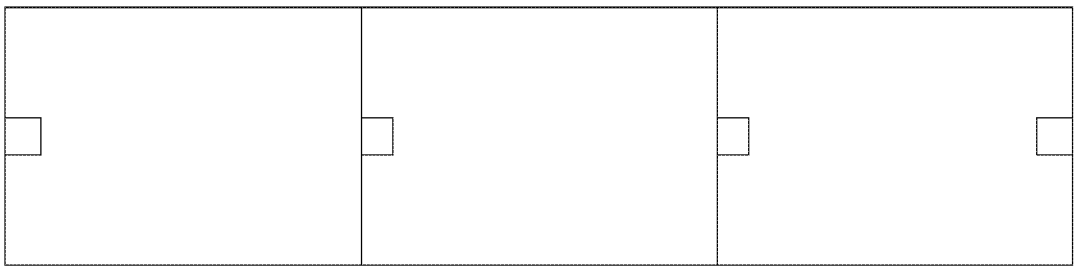
Question: Is a structure a greenhouse if some of its walls are porous or if some of its sides are removed?

Answer: If a greenhouse structure has sides/panels and a significant portion of the enclosure may be removed, such as large glass panels that are taken off, fiberglass or polyurethane walls which are moved up and down, sliding gateways that move back to essentially remove significant portions of the structure, or other similar apparatus where the non-porous sides/panels are removed, then such a structure would not be considered a greenhouse as long as the sides/coverings remain completely removed during the entire pesticide application and any applicable REI associated with the application is met. (February 28, 1995)

4-10 Greenhouses, one structure with 3 subenclosures

ED_001854_00008312-00010

Question: Is the structure illustrated below considered 1 greenhouse or 3 greenhouses?



1 range with 3 sections separated by walls and doors

Answer: This structure is one greenhouse consisting of three subenclosures, except in the rare circumstance that each section, including all ventilation systems, can be completely sealed off from one another. This question is most important when fumigants are applied in a greenhouse. In that instance, the WPS (and the fumigant label) prohibit entry to the entire greenhouse (including any adjacent structure or building that cannot be sealed off from the treated area) by any person, other than a trained and equipped pesticide handler performing certain handler tasks. The prohibition extends until the entry criteria listed on the fumigant's labeling are met.

For non-fumigant pesticides, the WPS permits the use in greenhouses of sub-enclosures that need not meet the stringent criteria of being "sealed off" from the rest of the greenhouse structure. Sub-enclosures can be created for non-porous wall, including temporary walls consisting of intact, sturdy plastic or other non-porous materials, that restrict the movement of non-gaseous pesticides to the area within. Such a sub-enclosure constitutes the area that must be vacated during smoke, mist, fog, and aerosol applications and during applications for which the pesticide labeling requires the applicator to wear a respirator, and also constitutes the area that must be posted.

In addition, if the treated area is so enclosed, the 25-foot setback zones for certain other types of pesticide applications do not extend beyond the walls of the sub-enclosure. (February 28, 1995)

4-11 Coarse spray, applicability to Tables 1 and 2 in 40 CFR part 170.110

Question: For the purposes of the restrictions during application in greenhouses and nurseries, is a coarse spray defined as one produced with pressures less than 40 psi? If so, is a coarse spray one of the "otherwise" types of applications in Tables 1 and 2 in 170.110, i.e., those applications where workers are prohibited only in the treated area and not in the larger area of the greenhouse or nursery during application?

Answer: The term coarse spray is not used in the regulation and therefore not defined. An "otherwise" type of application is one that does not meet the criteria in Column A, Tables 1 and 2, at Section 170.110, and is irrespective of droplet size. (June 14, 1996)

4-12 What is the treated area, when pesticide spray is directed to the base of a tree

Question: What is the treated area when a pesticide is applied by directed spray to the base of a tree in an orchard? Will the whole orchard be off limits to early entry by workers?

Answer: The treated area is the area to which the pesticide is directed. An agricultural employer may designate what the restricted entry area is by the appropriate notice of application. It is this designated area, not the whole orchard, to which the restricted entry interval applies. (June 14, 1996)

ED_001854_00008312-00011

4-13 Definition of enclosed cockpit

Question: How should an "enclosed cockpit" be defined, per CFR 170.240(d)?

Answer: An aircraft with an enclosed cockpit is defined as any aircraft with a windshield and adjoining canopy. Additionally, pilot points of entry and all windows must be closed. EPA recommends that, when possible and in accordance with Federal Aviation Administration regulations, air filters or positive pressure systems be installed on aerial application aircraft. (June 14, 1996)

4-14 Definition of contaminated aircraft

Question: The WPS requires the use of chemical resistant gloves to be worn by any person entering or leaving an aircraft contaminated by pesticide residues. How does EPA define the term "contaminated aircraft" as found in this provision?

Answer: For the purposes of 40 CFR 170.240(d)(6)(i), an aircraft will be considered contaminated any time after the aircraft has been used in applying a pesticide, even if there are no "visible" signs of contamination. The aircraft will be considered to be contaminated until such time that the aircraft has been rinsed or washed in a manner consistent with routine washing practices. The mixing and/or loading of pesticides into the aircraft mix tank shall not be considered to result in contamination of the aircraft as long as such mixing/loading is accomplished through a closed system or other mechanism that will not result in pesticide residues being deposited onto the aircraft. (June 14, 1996)

5 Entry Restrictions

5-1 State-established REIs

Question: If state-established REI's are put on labels, will early entry provisions apply?

Answer: If the label bears the WPS reference statement and a statement requiring compliance with a Restricted Entry Interval (REI), albeit one that was placed on the labeling to reflect a State-established REI, it is considered to be the restricted-entry interval required under FIFRA. Thus, the WPS provisions apply unless otherwise specified on the label. Please note that REI's on labeling must be reflected in the Federal registration of the product. If States impose an REI through State regulation which is not on the labeling, the State REI would not trigger the REI related provisions from the WPS. (March 22, 1993)

5-2(a) Irrigation activities

Question: Why are irrigation activities excluded from the definition of "hand labor" and yet only short-term entry is allowed?

Answer: Irrigation activities were excluded from the definition of "hand labor" in order to create a short term exception for such activities under the early entry provisions. Irrigation activities do pose exposure concerns, but the Agency recognized that these activities need to be done. The Agency requires protection from this exposure by limiting the amount of time a worker is allowed in the treated area and requiring the worker to wear PPE. (March 22, 1993)

5-2(b) Irrigation activities under an REI (continued)

ED_001854_00008312-00012

Question: Under what circumstances can irrigation take place during a restricted-entry interval (REI) (40 CFR §170.112)?

Answer: WPS was designed to reduce the opportunities for workers to be exposed to pesticide residues in treated areas during REIs. For example, with the exceptions noted below, irrigation pipe may not be moved during REIs when that task would bring workers into contact with treated surfaces. As a result, agricultural employers should schedule pesticide applications and irrigation so that the need for irrigation involving workers during REIs will be minimized. If, however, irrigation in a treated area under a REI is essential, it is permitted under WPS under the following conditions:

(1) Without Entry to Treated Area -- Some irrigation tasks take place at the edges of fields, which may not be within the treated area (area to which the pesticide has been directed.) An example may be the installation or removal of pipe for furrow irrigation. As long as such activities do not cause workers to enter the treated area, they may take place without time limit or use of personal protective equipment (PPE) during the REI.

(2) With Entry to Treated Area:

a. By Pesticide Handlers -- During chemigation or when pesticide labeling requires the pesticide to be watered-in, this task may be performed by trained handlers wearing the handler PPE specified on the product labeling. [See the Question and Answer on watering-in, found in the Handler Activities section of this document, for additional details].

b. By Workers With No Contact -- WPS provides an exception for entry to treated areas, after any inhalation exposure level or ventilation criteria have been met, without PPE or other time limitation, when there will be no contact with the pesticide or its residues [40 CFR §170.112(b)]. Note, however, that PPE cannot be used to prevent the contact under this exception. This exception may apply to a variety of typical irrigation situations, e.g.:

- Workers moving irrigation equipment or performing other tasks in the treated area after the pesticide was correctly soil-incorporated or injected, provided the workers do not contact the soil subsurface by digging or other activities.
- Workers walking or performing other tasks in furrows after the pesticides are applied to the soil surface in a narrow band on beds and there is no contact with those treated surfaces.

c. Short Term -- Workers may enter treated areas during REIs to perform short-term tasks [40 CFR §170.112(c)] provided that:

(1) such entry does not take place during the first four hours after application and until any inhalation exposure limits or ventilation criteria are met;

(2) the entry does not involve more than one hour per day per worker;

(3) the worker does not perform tasks defined in WPS to be hand labor (operating irrigation equipment is not hand labor under WPS, as stated at 40 CFR §170.3 under the definition of hand labor);

(4) the worker wears the early-entry PPE specified on the pesticide labeling;

(5) is correctly informed as required for early-entry workers in the WPS; and

(6) all other applicable requirements of 40 CFR §170.112 are met.

d. Agricultural Emergencies -- The WPS permits early entry by workers to perform tasks including irrigation while wearing early-entry PPE, and without time limits, in response to an agricultural emergency, as defined in the regulation at 40 CFR §170.112(d).

e. EPA-Approved Exceptions -- Section 170.112(e) of WPS permits exceptions to the general prohibition on work in treated areas during REIs when EPA has approved a special exception. Exceptions may be requested of EPA as described in that section of the regulation. (February 25, 1994)

5-3 Wet plants vs. REIs

Question: Are agricultural workers allowed to enter a treated area when the plants are wet if/when the REI specified on the label has expired?

Answer: In the past, labels have contained statements that said that reentry could take place "when sprays have dried, dust has settled, and vapors have dispersed."

The Agency established a 12-hour minimum REI labeling requirement in the WPS for agricultural use products. In addition, individual products within the scope of WPS may bear specialized labeling that address moisture.

However, in the case of a WPS REI of x number of hours and in the absence of additional instructions regarding wet plants, the agricultural employer would not be in violation if workers enter the field when the agricultural plants are wet provided the REI specified on the label has expired.

An REI specifying after sprays have dried, dust has settled and vapors have dispersed may still appear on products not within the scope of the WPS or for uses that are not within the scope of the WPS. In this case, entry may occur only if the sprays have dried, dust has settled or vapors have dispersed. Note, for products with WPS and non-WPS uses on the label that bear both the 12-hour minimum REI and the sprays dried, dusts settled and vapors dispersed language, the label should clearly indicate which REI applies to which use. (November 7, 1994)

5-4 Potting soil in pots

Question: If potting soil is treated with a pesticide in one location in a nursery or greenhouse and then placed in pots and used to produce plants in another area of the nursery or greenhouse, is the treated area the soil and therefore any REI restrictions would continue to apply in the second location?

Answer: Yes. The treated area is the area to which the pesticide was directed. In this case, the soil in the pots is the treated area. Therefore, any REI and associated requirements would continue to apply after the application. If the treated area is moved in containers, the REI and associated requirements are in effect for the treated area. (See question 14.23) (February 28, 1995)

5-5 Potting soil, movement off site

Question: If the treated soil is sold (in the pots with the crop) and moves off site, do any REI and other treated-area restrictions apply?

Answer: No. If the treated area in a pot with the crop is moved off the agricultural establishment, it is no longer covered under WPS. Therefore, no WPS requirements will apply at the new location. However, any label specific non-WPS REIs or other labeling restrictions must be met. (February 28, 1995)

5-6 Moving containers during REI

Question: If the soil/plants in pots are treated, can the container be moved during the REI?

Answer: Yes, the container may be moved provided there is no contact with the treated area by workers. If only the soil is treated and not the pot along with the soil such as in an overhead spray, then any REI restrictions apply only to the soil which has been treated. Moving the pot without any contact with the soil would not be in violation of the REI. If plants are treated, a worker can move containers provided there is no contact with the plants or other treated surfaces, and pesticides cannot drop or drip onto the worker. If the pesticide application is directed at the container and plant, then both are considered the treated area and are subject to any REI restrictions. In either of the above situations, the notification requirements, found at 40 CFR 170.120, apply to the treated area whether it is the soil/plant or the soil/plant and pot. (February 28, 1995)

5-7 Greenhouses, spraying 12 inches from planting medium

Question: The 40 CFR part 170.110 lists entry restrictions for greenhouses and nurseries associated with pesticide applications. One criterion for determining entry restrictions is spraying at a height of greater than 12 inches from the planting medium. In greenhouses with hanging baskets, is the 12 inch height measured from the top of the medium?

Answer: Yes. (February 28, 1995)

5-8 Entry under an REI for no-contact activities

Question: May an unprotected worker enter a treated area under an REI immediately after the application if it is for activities with "no contact"?

Answer: Yes. An unprotected worker may enter a treated area immediately after the application is finished as long as any inhalation exposure level or ventilation criteria listed on the labeling has been reached, and he will have no contact with anything that has been treated with pesticide including pesticide residues on plants, on or in the soil, in water, or in the air. (March 7, 1995)

5-9 Greenhouse applications, when does REI begin

Question: Does the Restricted Entry Interval (REI) for a greenhouse application begin upon completion of the application (once the pesticide is no longer being distributed) or only after the ventilation criteria have been satisfied?

Answer: The REI begins upon completion of the application. The REI and ventilation criteria are independent of each other. No person, other than a properly trained and equipped handler may enter a greenhouse until the ventilation criteria, if applicable, have been met. [See 40 CFR part 170.110(c).] (March 7, 1995)

ED_001854_00008312-00015

5-10 Irrigation in arid areas

Question: Does the WPS offer WPS flexibility to restricted entry intervals when growers use irrigation in arid areas?

Answer: No. Irrigation does not affect the definition of an arid area which is defined as less than 25 inches of rainfall a year. Thus, if the REI for organophosphates is 72 hours in arid areas, a grower could not use irrigation to reduce the REI to 48 hours. (March 7, 1995)

6 Equivalency Issues

6-1 Protocol for state regulatory equivalency

Question: Will EPA consider regulatory equivalency on specific worker protection elements if requested by a state? If so, what protocol must be followed?

Answer: The Federal worker protection standard sets a national minimum, with states permitted to set more stringent standards. While the regulation does not specifically include provisions for accepting regulatory "equivalency," we intend to use a common sense approach to assessing these issues on the basis of whether such differences should be approved if they provide equivalent or enhanced protections of workers and handlers as outlined below.

States which have their own worker protection regulations may have requirements which are: 1) identical to the Federal standard; 2) different than the Federal standard but the state requirements include strict compliance with the Federal requirements; or 3) different than the Federal standard and the state requirements do not include strict compliance with the Federal requirements but which may provide equivalent protection. Each of these scenarios are discussed below.

(1) Identical requirements - This scenario should present few, if any, problems. If questions arise regarding the interpretation of state regulations which are identical to the Federal regulations, the state should consult with the Regional office, in order to avoid conflicts between a state's interpretation of the regulation and EPA's interpretation of identical language. Issues not easily resolved should be elevated by the Regional Office to the Worker Protection Standard Interpretive Guidance Workgroup for resolution.

(2) Different requirements which include strict compliance with the Federal requirements - In this situation, the state may have different requirements which are more stringent than and which meet the Federal standard. In meeting the state requirement, a person automatically is in strict compliance with the Federal requirement. An example of this would be a state restricted entry interval (REI) of ten days imposed by state regulation (restricting entry to at least the same degree as the WPS) as compared to a Federal REI of three days. Compliance with the state REI also complies with, or exceeds, the Federal REI.

Questions which arise for this scenario usually involve whether or not a state requirement does include strict compliance with the Federal requirement. In those cases where a state is unclear as to whether or not compliance with the state requirement would include strict compliance with the Federal requirements, EPA will be available to discuss these issues with the state. Cases which cannot be resolved by the Regional Office may be elevated through the sublead Region to the Interpretive Workgroup for consideration.

(3) Different requirements which do not include strict compliance with the Federal requirements but which may provide equivalent protection - The worker protection standard does not provide for the imposition of

ED_001854_00008312-00016

different requirements in place of the Federal requirements. In those situations where the state has different requirements which do not include strict compliance with the Federal requirements, the Federal requirements remain in effect in that state, as do the state requirements. States may find it useful to publicize a list of those provisions under EPA's worker protection standard which are not met by complying with state law.

However, in those situations where a state wants EPA to allow such a state requirement in lieu of a Federal requirement because the state believes that the state requirement provides equivalent or better protection, the state may make such a request. The EPA could allow this through an amendment to the regulations, or through programmatic interpretive guidance, or, in certain situations, through enforcement discretion. While it is possible to grant enforcement discretion, this is not usually done except on a temporary basis when the original rulemaking did not consider and address a particular issue and a more permanent solution is anticipated through an amendment to the regulation or modification to state law.

To request the Agency to undertake rulemaking, or issue interpretive guidance, or grant enforcement discretion, a request should be submitted which addresses: (1) specific provisions in the Federal regulation and the corresponding state requirements for which the state believes its approach provides equivalent or better protection; (2) why it believes that equivalent or better protection is provided under the corresponding state requirements; (3) any facts that it believes were not considered at the time of rulemaking; (4) any other information relevant to the need for the change; and (5) the impact if the requirement is not modified. The request should be sent to the Regional Office, who should then forward it to the sublead Region for submission to the Worker Protection Standard Interpretive Guidance Workgroup. The Workgroup will review the request and present it to EPA's management for consideration. (March 29, 1993)

6-2 California's use reporting requirements

Question: Do California's use reporting requirements meet the standards and intent of the Federal worker protection elements?

Answer: It is our understanding that this question deals with EPA's requirement to display application information in a central location and whether California's use reporting requirements would be considered as "equivalent." California's position is that they require records be kept by the grower and made available on request. It is our understanding that these records require the name of the pesticide. However, it is unclear whether this means the active ingredient(s) and/or the product (brand) name of the pesticide; the WPS requirements require listing the product (brand) name and active ingredient(s) of the pesticide. In addition, the California regulations do not require records on the Restricted Entry Interval (REI), as required to be displayed according to the WPS.

The issue of whether to require the display of application information as opposed to providing it on request was examined during rulemaking and responded to. Based on our understanding, the California requirement does not include displaying the information which is required under the Federal WPS. As discussed, displaying this information was considered a key element in assuring the information is easily available to workers.

As a result, California's existing requirement does not appear to fully satisfy either the WPS requirements or EPA's intent in developing the regulation. (March 29, 1993)

ED_001854_00008312-00017

7 Exemptions/ Exceptions

7-1 Growers/owners applicability of WPS

Question: Are growers (owners) personally subject to the REI provisions, entry restrictions, and PPE requirements for early entry activities?

Answer: Yes, growers (owners) are personally subject to the REI provisions, entry restrictions, and PPE requirements for early entry, when using a product referencing the WPS. (March 22, 1993)

7-2 Exception requests, irrigation activities

Question: Will the Agency consider a request for approval for an exception to the 1 hour/24 hour requirement for irrigation activities?

Answer: Yes, the Agency will consider a request provided such a request is submitted pursuant to 40 CFR part 170.112(e)(1). (March 22, 1993)

7-3 Self-employed persons, applicability of WPS

Question: The definition of a "worker" includes a self-employed person. Does this mean that growers are required to comply with all provisions where they are not specifically exempt?

Answer: In general, self employed people who perform worker activities must provide themselves with the protections required for workers. However, if they qualify for the agricultural owner exemption, they are exempt from some provisions. (March 22, 1993)

7-4 Small establishments, applicability of WPS

Question: Are small agricultural establishments exempted from compliance with the Worker Protection Standard?

Answer: No. Except for a partial exemption for owners and their immediate families (immediate family includes only spouse, children, stepchildren, foster children, parents, stepparents, foster parents, brothers, and sisters), all agricultural establishments that use pesticides that have WPS labeling must comply with the Standard when using those products for uses within the scope of the WPS. (March 22, 1993)

7-5 Exemptions to provisions on the label

Question: Section 170.120(a)(3) and (b)(3) exempts the employer from the label provisions for notification if the workers do certain activities. This appears to be in direct conflict with any label requirement and may confuse the regulated public as well as create enforcement problems. Please clarify the apparent conflict.

Answer: Your observation can best be clarified by referring to Section 156.206(b)(2) which states that "Each product shall bear the statement: "This standard contains requirements for the protection of agricultural workers on farms, forests, nurseries and greenhouses, and handlers of agricultural pesticides. It contains requirements for training, decontamination, notification and emergency assistance. It also contains specific instructions and exceptions pertaining to the statement on this label...about...notification to workers."

ED_001854_00008312-00018

Therefore, the labeling would allow for exceptions in these cases. (March 22, 1993)

7-6 Moving contaminated irrigation equipment

Question: The definition of "hand labor" excludes the handling, operation or repair of irrigation equipment. Does this mean workers who move contaminated pipes do not have substantial exposure and are therefore exempt from the early entry restrictions?

Answer: No, they are subject to the early entry restrictions. However, note that there is a specific early entry exception called the "short term" exception for such activities. (March 22, 1993)

7-7 Wide-area public pest control programs

Question: Does the exception from WPS for "wide-area public pest control programs" extend to those cooperative programs in which the growers themselves make or arrange for pesticide applications to their crop areas?

Answer: No. The exceptions at 170.12(b)(1) and 170.202(b)(1) do not extend to those cooperative programs in which the growers themselves make or arrange for pesticide applications to their crops.

WPS clearly applies to applications made under the control of an agricultural employer "on an agricultural establishment in the production of agricultural plants," regardless of whether the applications are also part of a program involving a governmental organization. Examples of such applications are boll-weevil or gypsy moth applications which the growers themselves arrange for or make. (February 24, 1994)

7-8 Immediate family exemption

Question: Please explain the immediate family exemption, i.e., are wholly family owned agricultural establishments are exempt from the WPS; how does the immediate family exemption apply when there is more than one owner, related or unrelated?

Answer: Wholly family owned agricultural establishments must comply with the WPS. However, the revised final rule exempts owners of agricultural establishments from providing to themselves, and to members of their immediate family, some of the requirements of the rule. (40 CFR parts 170.102(c) and 170.202 (c))

The rule defines immediate family as including only spouse; children; step children; foster children; parents; stepparents; foster parents; brothers; and sisters. (40 CFR part 170.3)

In general, owners are exempted from providing themselves or members of their immediate family the following:

- safety training and information;
- providing, cleaning, and maintaining personal protective equipment;
- information at a central location;
- decontamination facilities;
- notification of pesticide applications; and
- emergency assistance.

A person does not qualify as an owner for purposes of the exemption if he/she has rented or leased out their farm, forest, nursery, or greenhouse to another person and has no part in the management of or profit/loss from

ED_001854_00008312-00019

the establishment (in such a case, the person to whom the establishment has been rented is considered the "owner"), or if he/she has been hired to operate a farm, forest, nursery, or greenhouse and the person who owns the property shares in the profits or losses from the property. Persons who operate, but do not own, an agricultural establishment do not qualify for the exemption.

The exemption applies to owners without regard to whether the owner has incorporated or otherwise organized for business purposes.

In situations where two or more persons own an agricultural establishment, the exemption applies to the owners if each owner is related to every other owner as an immediate family member or as an in-law. In addition, all members of each owner's immediate family are eligible for the exemption.

Exception: If owner "A" is the parent of owner "B" and the grandparent of owner "C", all three qualify for the exemption as long as they are related to every other owner in one of the eligible relationships.

For example, the exemption will be available to a brother, sister, and the sister's spouse who jointly own an agricultural establishment. The owners need not provide some of the provisions required by the rule to themselves or to the children, parents, or siblings of each owner. Technically, under a very strict reading of the rule, the children of one of the partners would be nieces or nephews of the other partner and the corporation would not be allowed the immediate family exemption. However, in this type of example, the spirit of the immediate family exemption is still being met. Similarly, the exemption will not be denied if the ownership consists of a husband, wife and the wife's parents, or consists of a parent, child and grandchild.

In other words, when an agricultural establishment is owned by more than one person, the exemption is available to the owners ONLY if each owner is related to each other owner in one of the following ways:

- spouse,
- child, stepchild, foster child, son-in-law, daughter-in-law,
- parent, stepparent, foster parent, parent-in- law,
- brother, brother-in-law,
- sister, sister-in-law,
- grandparent-parent-grandchild exception explained above.

If the owners are each related to one another in one of the above specified ways, then the owners need not provide certain protections to themselves or to any member of any owner's immediate family.

In situations where all of the owners are not related in one of the above specified ways, e.g., two brothers and a neighbor; or the owners are the grandparent and grandchild when the parent of the grandchild is not also one of the owners, none of the owners qualifies for the agricultural owner exemption and each owner must provide all WPS protections to those persons not in their immediate families and to each other.

Although owners of establishments and members of their immediate family are exempt from some of the provisions of the rule, there is no reason they cannot follow those revisions and EPA encourages owners and family members to provide themselves and each other with these protections. These individuals also need to recognize that they are obligated to follow the other applicable provisions of the rule, including product-specific requirements on pesticide labeling such as restricted entry intervals (REIs) and personal protective equipment (PPE). Finally, if an owner employs both family members and non-family members to work on the agricultural establishment, the owner must provide the non-family members with all of the protections included in the rule.

ED_001854_00008312-00020

NOTE: This interpretation is consistent with the exemption for family business under the Department of Labor's Migrant and Seasonal Agricultural Workers Protection Act (MSPA). (February 24, 1994)

7-9 Fire ant control/quarantine, potting soil

Question: Does the exception from WPS for "wide-area public pest control programs" extend to the treatment of potting soil as part of a fire ant control/quarantine program?

Answer: No. The WPS does apply to the treatment of potting soil for fire ant control/quarantine programs. The wide-area public pest control exception does not extend to cooperative programs in which the growers themselves make or arrange for pesticide applications. WPS applies to applications made under the control of an agricultural employer "on an agricultural establishment in the production of agricultural plants", regardless of whether the applications are also part of a program involving a governmental organization. (See the question and answer on wide-area public pest control programs, 7.16) (February 28, 1995)

7-10 Agricultural emergencies, is SLA only agency with authority to declare emergency

Question: Is the State Pesticide Lead Agency the only agency with the authority to declare the circumstances that could cause an emergency under the provisions found in section 170.112(d)?

Answer: No, the State Lead Agency for pesticides is not the only agency with the authority to declare the circumstances that could cause an agricultural emergency, but it is the agency responsible for determining if compliance has occurred. (March 15, 1995)

7-11 Agricultural emergencies, who can declare one when there is no clear authority

Question: For those situations where there is no agency with the authority over the circumstances that could cause an agricultural emergency, who can declare that circumstances exist that could cause an agricultural emergency?

Answer: If there is no separate agency with jurisdiction, the authority rests with the State Lead Agency responsible for pesticide programs. For situations where the heating or cooling system goes off in a greenhouse, the emergency arises not from the system going off but from the outside temperatures and for which the National Weather Service has jurisdiction. Thus, there is an agency with jurisdiction in such a situation. (March 15, 1995)

7-12 Agricultural emergencies, can SLA require documentation of emergency

Question: Can the State Pesticide Lead Agency require documentation of an agricultural emergency?

Answer: The Federal WPS does not require records to document the agricultural emergency. A State may promulgate regulations under State authority to require documentation. (March 15, 1995)

7-13 Agricultural emergencies, is there a violation if workers enter and emergency does not occur

Question: If a circumstance which could cause an agricultural emergency such as a freeze is predicted, and it does not occur, is there a violation if the agricultural employer sends workers into the treated area during an REI?

ED_001854_00008312-00021

Answer: No, there is no violation provided all other conditions in part 170.112(d) are met. There would be a violation if the employer sends workers in after he knows the circumstances are no longer in existence. (March 15, 1995)

7-14 Agricultural emergencies, may SLA declare circumstances which constitutes an emergency

Question: The regulation provides for an exception to the entry restrictions for an agricultural emergency at section 170.112(d). Along with other criteria that the agricultural employer must meet, one criterion is that a State, Tribal, or Federal Agency having jurisdiction declares the existence of circumstances that could cause an agricultural emergency on that agricultural establishment. May a State Lead Agency identify conditions which would constitute an agricultural emergency and set up procedures to avoid having to make the declaration on a case by case basis prior to the exception being utilized?

Answer: Yes. The State may handle the declaration of circumstances that could cause an agricultural emergency on an agricultural establishment in a number of ways. The State could declare through guidance or regulations the circumstances that could cause an agricultural emergency and for which early entry would be allowed provided the circumstances occur or are predicted to occur.

Please note that even if guidance or regulations are developed, the agricultural employer must ensure that the other requirements for this provision are also met prior to sending workers into the treated area before the end of the restricted entry interval, e.g., the agricultural emergency could not have been anticipated, the employer would suffer a substantial economic loss without entry, and that no alternative practices could have prevented or mitigated a substantial economic loss, as defined in the WPS. EPA is willing to work with the States to develop this guidance. (March 15, 1995)

7-15 Exemptions for workers entering a treated area, applicability to pesticide handlers

Question: Do the requirements/exemptions for workers entering a treated area before an REI expires set out in section 170.112 also cover pesticide handlers since they are defined in the standard as persons who apply pesticides and may have to go into fields under an REI?

Answer: No. Pesticide handlers (employees applying, mixing, or loading pesticides, cleaning, repairing, etc.) may enter fields during an REI provided label-specified PPE is worn and the activity being performed is a handler activity. (June 14, 1996)

8 Generic Requirements

8-1 Access to the 40 CFR part 170 requirements

Question: How will employers and applicators have access to the Part 170 requirements that are not specified on the label?

Answer: It is the responsibility of the employer to comply with the regulation. However, we believe our efforts to widely disseminate information about the regulation will facilitate compliance with the requirements of the regulation.

In addition, the Agency is preparing a "How To Comply" manual, which is an "everyday English" version of the worker protection standard. This manual is designed to contain everything that an affected employer will need to

ED_001854_00008312-00022

know in order to comply with the 1992 WPS. GPO will print and sell the manual. Also, several private organizations have indicated they intend to print and sell copies of the manual. (March 22, 1993)

8-2 Transportation to medical facility

Question: Is an agricultural employer in violation of the WPS if he refuses a worker transportation to a medical facility if to the best of the employer's knowledge, the worker's symptoms do not suggest pesticide poisoning?

Answer: Yes, provided that a product with WPS labeling has been used and exposure to the worker could have occurred on the agricultural establishment, and there is a claim of pesticide poisoning or injury by exposure to pesticides. The Agency considers this situation to be sufficient reason to believe that the worker may have been poisoned. Thus, transportation to a medical facility needs to be made available by the agricultural employer.

Please note that while a worker's symptoms may not suggest pesticide poisoning to the employer, there are many symptoms of pesticide poisoning that could be misconstrued with the symptoms of other illnesses, e.g., the flu. (February 28, 1995)

8-3 Return transportation from medical facility

Question: Is an agricultural employer required to provide return transportation from a medical facility to a worker?

Answer: No. The WPS requires that the agricultural employer make available transportation from the place of employment to the medical facility. It does not require that transportation be provided back to the place of employment. (February 28, 1995)

8-4 Who pays for transportation to medical facility?

Question: When transportation is required for emergency assistance, who is responsible for paying when there is a charge for the transportation--the employer or the employee?

Answer: The employer is responsible for providing transportation, which would include paying when there is a charge for transportation. (March 15, 1995)

8-5 Agricultural employer transportation requirements for migrant workers

Question: The regulations pursuant to the Migrant and Seasonal Agricultural Worker Protection Act (29 USC 1801 et seq.), as amended, set forth specific requirements that agricultural employers must meet before transporting migrant or seasonal agricultural workers. The regulations are apparently applicable to any employer who transports workers. The WPS requires agricultural employers to provide emergency transportation for a worker under certain circumstances. This is an apparent conflict as this may cause an employer to be in violation of the above Act if they transported a worker in a vehicle that did not meet the safety/insurance requirements set forth in the pursuant regulations. How will agricultural employers comply with the emergency transportation requirements of the WPS without violating another existing Federal regulation?

Answer: There is no conflict in the above mentioned regulations. Agricultural employers must comply with all applicable Federal and State laws and regulations pertaining to their operations. The WPS requires agricultural employers to "make available" emergency transportation for employees under certain circumstances. An

ED_001854_00008312-00023

agricultural employer must also comply with other laws or regulations that may govern the transportation of workers. (June 14, 1996)

9 Handler Activities

9-1 Watering-in

Question: When a pesticide product's labeling contains directions for watering-in (or indicates that irrigation should take place) after application, may watering for that purpose be performed by handlers under WPS?

Answer: When a label requires or advises watering-in of a pesticide it is considered to be part of the application. Entering a treated area to water-in when the label requires or advises it is a form of soil incorporation that may be performed at any time by trained handlers wearing the handler PPE specified for the pesticide on its labeling and provided with other handler protections. Handlers may perform such watering-in tasks in the treated area and without time limit when it is required or advised by the label. Although watering-in may be done through irrigation, it is important to note that routine irrigation of crops is not considered to be a handler task under WPS. (February 25, 1994)

9-2 Access to product labeling

Question: The preamble discussion on 40 CFR part 170.232 does not require the employer to make multiple copies of the label or the handler to carry a copy of the label during the handling activity. What are the requirements of "access to the product labeling information during handling activities?"

Answer: The Agency interprets this phrase to mean that the product labeling information is accessible to the handler for reference should the handler have questions about the handling, mixing or application of the product or need to seek further information on the product. This does not mean that the handler must carry a copy of the product label. It does mean that the handler should know where to find a copy of the product label information and that the product label information is available to the handler during the time he is performing handler activities. (March 7, 1995)

10 Labeling Issues

10-1 Compliance with language referred to on labeling

Question: Section 2(p) of FIFRA states that current official publications of EPA are not labeling. The new WPS regulations appear to be official publications in that they are printed in the FR and therefore cannot be considered "labeling." Please elaborate on this issue.

Answer: The label specifically states in the Directions for Use section that users must comply with the WPS. Therefore, a violation of the WPS would be use inconsistent with the label. Thus, because we are basing enforcement of the WPS on the fact that compliance with the Standard is required by a use direction on the label, it is not material whether the WPS itself is, or is not, considered labeling. (March 22, 1993)

10-2 Old versus new label requirements

Question: If a user has possession of both an old product (i.e., without the WPS statements) and a label with the new standards, which PPE requirements apply?

ED_001854_00008312-00024

Answer: When using a product which does not bear the WPS reference, the label of the product being used applies and compliance with the WPS is not required. Please note that the label on the product at the time it is sold/distributed is the governing label. If products are being combined, e.g., in a tank-mix, and one product bears the WPS reference and the other does not, the more stringent requirement must be met. Following the WPS requirements in addition to the label requirements would not cause a violation. (March 22, 1993)

10-3 Sale and use of non-WPS labeled products after October 23, 1995

Question: A pesticide dealer operates a pesticide application service out of the same establishment. The total bill for the application services usually includes the cost of the pesticides (obtained through the dealership) and the fee for application, but they are separate line charges on the bill. If the dealer continues to apply non-WPS labeled products commercially in this manner after October 23, 1995, does this constitute illegal sale of and/or distribution of a pesticide?

Answer: No product to which WPS applies may be sold or distributed without WPS labeling after October 23, 1995. Applying a registered pesticide for hire is not sale and distribution under FIFRA provided that the product is applied by the dealer or his employee and none is left behind for the customer. Therefore, if an applicator applies a registered non-WPS labeled pesticide after October 23, 1995, this will not constitute illegal sale and distribution of a pesticide based on its lack of WPS labeling. This is true regardless of the billing provided the product was correctly labeled prior to the required dates and is not a bulk pesticide delivered after April 21, 1993. (Bulk pesticides are subject to the dates applicable to registrants.) (March 7, 1995)

11 Notice of Application

11-1 Premises, definitions

Question: Section 170.120(d) requires notification before an application "If a worker will be on the premises during the application..." What is the meaning of "premises"?

Answer: The term "premises" means the agricultural establishment. (March 22, 1993)

11-2 Oral notification

Question: Under section 170.120(d) how close to a treated area must a worker be for oral notification to be given?

Answer: An oral warning must be given:

On farms, forest, or nurseries - to any worker who may be in a treated area or walk within 1/4 mile of the treated area during a pesticide application or while an REI is in effect;

In greenhouses - to any worker who may be in a greenhouse during a pesticide application there or while an REI is in effect in that greenhouse. (March 22, 1993)

11-3 Adjacent properties

Question: In cases where different property owners have treated areas adjacent to each other, are they both required to notify workers if they are within 1/4 mile of both properties?

ED_001854_00008312-00025

Answer: No, the rule requires agricultural employers to notify only their own worker-employees. (March 22, 1993)

11-4(a) Notification of application

Question: The WPS requires that employers of pesticide handlers provide information to the agricultural employer about the pesticide before it is applied. What provisions apply if the pesticide cannot be applied as scheduled?

Answer: Section 170.224 of the WPS requires that specific information be provided by the handler employer to the agricultural employer about pesticide applications on the agricultural establishment before the application has taken place so that the agricultural employer can in turn provide appropriate protection to his workers and family. The Agency is aware, however, that some applicators may on occasion not be able to perform pesticide applications at a previously-scheduled time. The How-to-Comply Manual provided some flexibility on this issue, noting that "if the pesticide is not applied as scheduled, the agricultural employer must be informed of the corrected time and date of the application. Make the correction before the application takes place, or as soon as practicable thereafter." Questions have arisen concerning the notification requirements if applications do not take place as scheduled, including when and how the employer must be notified of the change.

The WPS places certain requirements upon agricultural employers. One of the most important requirements involves keeping workers out of treated areas during applications and while the REI remains in effect, and providing workers with (among other things) information, protective equipment, and decontamination supplies when they enter treated fields within thirty days of expiration of the REI. The requirement for applicators to notify agricultural employers before an application takes place must be viewed in light of its central purpose: to provide employers with information they may need in order to provide protection to agricultural employees.

The obligation of employers to assure that workers remain out of treated areas during applications and while the REI remains in effect, and to assure that proper protection are provided when workers enter treated areas within thirty days of expiration of the REI, is not affected by the notification provision; the obligation of the employer continues whether or not notification of an application occurs. The employer should therefore take whatever steps are necessary to assure that he/she is informed of an application before workers might enter treated areas.

Obviously, notification prior to application is the best means to assure that the employer has the necessary information to provide protection to his/her agricultural employees. For this reason, the WPS requires that notification take place prior to applications. Applicators are liable under the WPS if they fail to provide such notification.

EPA recognizes that there may be circumstances where an application does not take place when scheduled, and where communication between applicator and agricultural employer may be difficult to accomplish. The Agency is therefore willing to allow some rescheduled applications to go forward without requiring prior notification of the rescheduled application. This flexibility is available only in circumstances where an application has been previously scheduled (including day, date, and time) and agreed upon by the applicator and agricultural employer, the prior notification required by the WPS has been provided, and the pre-arranged application subsequently does not take place as scheduled. Notification by the handler employer to the agricultural employer of the application must occur as soon as practicable after the rescheduled application, and must occur within 24 hours of the rescheduled application.

Applicators and employers must keep in mind that the agricultural employer is still liable if employees enter fields during the REI, or within 30 days of expiration of the REI if any applicable WPS requirements are not met.

ED_001854_00008312-00026

Notification must either be received by the agricultural employer before workers could be exposed to pesticide residues resulting from the application in violation of the WPS or the applicator must have notified the employer with a form of notification previously agreed upon by the applicator and agricultural employer which was reasonably calculated to get information to the employer before workers could be exposed to residues in violation of the WPS.

EPA strongly recommends that applicators and employers workout in advance between themselves how notification of regularly scheduled applications should be accomplished, under what circumstances applications may take place without prior notification if previously scheduled applications do not occur on time, and how notification of rescheduled applications should be accomplished. (February 28, 1995)

11-4(b) Notification of application, information regarding application

Question: Section 170.224 of the WPS requires that before the application of any pesticide on an agricultural establishment, the handler employer must provide or must assure that any agricultural employer for the establishment is aware of certain information regarding the pesticide and the application. For purposes of section 170.224 of the WPS, what constitutes compliance with this requirement?

Answer: EPA recommends that the agricultural employer and the handler employer agree on a notification process that will ensure that workers will not be in an area while it is being treated or under an REI. For example, the employers could agree:

- that without prior mutual agreement, an application will never occur before the scheduled time, and
- the agricultural employer will not permit workers into the area to be treated until he/she receives notification from the handler employer that:

  (a) either the application will not take place until a specified future time at the earliest, or

  (b) the application has taken place and specific information required by Section 170.224 is provided to the agricultural employer.

Examples of compliance:

(1) An oral exchange of the required information between the handler employer and agricultural employer prior to an application would comply with the notification requirements of the WPS;

(2) Leaving a complete message on a telephone answering machine prior to the application would constitute compliance if the message was actually received by the agricultural employer prior to the application.

(3) Leaving a complete message on the answering machine prior to the application would constitute compliance if the handler employer and agricultural employer had agreed that by leaving a complete message on the answering machine notification could be accomplished. In this example, the handler employer would have satisfied his/her obligations under the WPS even if the message was not checked by the agricultural employer prior to the application. The employer, however, would remain responsible if workers were sent into treated areas in violation of any portion of the WPS. (February 28, 1995)

ED_001854_00008312-00027

11-4(c) Notification after application

Question: If the initial notification of an application cannot be made because of difficulty in reaching the agricultural employer, can notification be made after application?

Answer: No. There are no provisions for allowing notification after application due to difficulty in contacting the agricultural employer initially. (February 28, 1995)

11-5 What is the treated area?

Question: In some areas, fields are so large that it may take days to treat the entire field. What is the "treated area" then, the whole field, or just the part treated each day?

Answer: The treated area is the portion of the field where the pesticide is directed. Employers may choose to designate only the areas being treated that day or previously treated as the treated area. Areas designated as treated and still under the REI requirements need to be posted if posting is required by the product labeling or the agricultural employer chooses to use posting as the means of notifying workers working within a quarter mile of the treated area. The whole field may be posted, but the field must remain posted until the REI expires for every section of it or specific posting is done for the sections remaining under the REI. Worker entry, other than that permitted under 40 CFR part 170.112, is prohibited for the entire posted area while the fields are posted. Posting of untreated areas may be deferred until the day that treatments will occur. (February 28, 1995)

11-6 Timing of notification

Question: How soon before an application must a handler employer provide the information to the agricultural employer as required by 170.224?

Answer: The WPS requires in 170.224 that the information be provided by the handler employer to the agriculture employer any time before the application takes place. (February 28, 1995)

12 Personal Protective Equipment (PPE)

12-1 Enclosed cabs

Question: Section 170.240(d)(5) specifies that enclosed cabs can be substituted for certain label-required PPE. This regulation allows either the manufacturer or a governmental agency to declare respiratory protection equivalency. This standard allows "self-certification" by the enclosed cab manufacturer and appears to be less restrictive than that provided by EPA Compliance Program Policy No. 12.6 that provides for state approval of such cabs upon the submission and review of data. Please explain the reason and purpose for the change between the policy and regulation. How can enforcement agencies, handlers, or employers be assured there is an adequate protection factor for manufacturer-certified cabs? In addition to the protection equivalency, must these engineering devices also meet the descriptive "definition" of enclosed cabs? The Department is aware of at least one manufacturer that has stated their intention to self-certify a cab that we believe does not meet the basic federal definition of an enclosed cab. The Department does not have any data on the respiratory protection factor accomplished by this cab.

Answer: The Federal regulation does allow for self-certification by enclosed cab manufacturers. The Agency made this a performance based standard in order to reduce the burden to states by not requiring licensing and

ED_001854_00008312-00028

certification by states. States, however, can certainly be more restrictive and prohibit self-certification under state authority. (March 22, 1993)

12-2 Chemical-resistant footwear

Question: Section 170.240(6)(i-iii) specifies the types of chemical-resistant footwear that may be worn. What is the difference between "chemical-resistant shoes" and "chemical-resistant boots"? If footwear has a rubber bottom and leather upper, is it considered a chemical-resistant shoe or boot?

Answer: This language allows the use of chemical-resistant shoes rather that requiring the use of high-top boots. Footwear with leather uppers would not be considered chemical-resistant. The entire shoe or boot must be chemical-resistant. (March 22, 1993)

12-3 Protective eyewear

Question: Can the protective eyewear provision of section 170.240(c)(7)(i-iv) be applied to current product labels that state something such as "wear goggles or a face shield"?

Answer: No, the Worker Protection regulation only applies to products whose labels reference the WPS. (March 22, 1993)

12-4 Clean changes of clothes

Question: How many clean changes of clothes are required to be at a handler decontamination site?

Answer: The handler employer must provide one clean change of clothes at each decontamination site for use in an emergency. This change of clothes may be one-size fits all coveralls. The requirement for one clean change of clothes is not for each handler but for each site, and is irrespective of the number of handlers at the work site. (40 CFR 170.250) (March 22, 1993)

12-5 Eye protection for dilute formulation

Question: If a product is being applied for which the label requires eye protection because of the hazard of the concentrated formulation, and the diluted formulation does not pose the same hazard, is eye protection required for the persons using the diluted formulation?

Answer: The answer depends on the labeling. Products may provide separate instructions for PPE for activities involving the concentrate. If such a distinction is made, the label(ing) would state the PPE that is required for mixing and loading and also for handling activities. If the label(ing) makes no distinction, the protective eye-wear listed on the label(ing) must be worn for all handling activities involving either the diluted or undiluted product. (February 28, 1995)

12-6 Disposal of drenched clothing

Question: Are drenched clothing in this rule which must be disposed of required to be disposed of according to RCRA?

ED_001854_00008312-00029

Answer: Drenched clothing may have to be disposed of according to RCRA regulations. The requirements depends on the individual circumstances. Appropriate State hazardous waste officials should be contacted for information on specific requirements. (March 7, 1995)

12-7 Applicability of enclosed cab restrictions

Question: Once PPE is worn in a treated area, it may not be worn into or taken into a cab. Does this prohibition also apply to mixers and loaders of pesticides driving application equipment?

Answer: Yes, the prohibition applies assuming that the application equipment in question is referring to the enclosed cab exception provision under the rule, [section 170.240(d)(5)]. If the mixers and loaders are driving application equipment, they are subject to the same requirements as the applicator regarding the enclosed cab and PPE. (March 7, 1995)

12-8 Enclosed cabs, exiting cab for no-contact activity

Question: If an applicator must exit his enclosed cab during an application, is he required to wear any PPE including a respirator, if he will not contact any pesticide treated surfaces in the treated area?

Answer: During the application, the applicator must wear the PPE required on the label(ing). Handlers must wear PPE when leaving the cab only if they will contact pesticide-treated surfaces in the treated area or if label specific prohibitions apply. They may leave the cab for a rest stop or other reason (other than handling pesticides) without wearing PPE if they will not be in contact with pesticide-treated surfaces in the treated area. The applicator may leave the cab and walk away from the just-treated area without PPE. (March 7, 1995)

12-9 Storage of PPE "apart" and "away"

Question: The rule requires that all clean PPE be stored "apart" from the pesticide contaminated area. It also states that workers have clean places "away" from pesticide storage and use areas to store their clothing not in use, etc. From an enforcement standpoint, what is meant by the terms "apart" and "away"?

Answer: The objective for this provision is to assure that clean PPE and personal clothing will not come in contact with pesticide residues. As long as the employer can assure that changing of clothes and storage of PPE occurs in an area separate from pesticide storage and use areas (including mixing and loading) so that these activities will not result in personal clothing or PPE coming into contact with pesticide residues, then the employer has met the criteria for "apart" and "away."

Ideally, this requirement may be met by providing a separate room for storage of PPE and changing activities; but there are a number of other ways of achieving compliance provided that pesticide residues do not come into contact with the PPE or personal clothing such as storing PPE in sealed containers. (March 7, 1995)

12-10 Heat stress; prevention when wearing PPE

Question: The requirement that employees wear PPE during application and the REI might pose a greater health risk from heat stress than pesticides themselves. How will this be handled?

Answer: Under WPS, employers have a responsibility to ensure that handlers and early entry workers: 1) wear the required PPE while in the treated area; 2) are not allowed or directed to perform activities without implementing measures to prevent heat stress; and 3) are trained in a manner they can understand in how to prevent, recognize

ED_001854_00008312-00030

and treat heat-related illness. EPA has developed A Guide to Heat Stress in Agriculture which provides guidelines on preventing heat stress.

NOTE: Entry during an REI is permitted only in strictly limited circumstances/exceptions. (June 14, 1996)

13 Posting signs/Display of Information

13-1 Modifications to posting signs

Question: Do states have authority to adopt their own posting sign format or require additional information?

Answer: States cannot modify the WPS required elements of the signs. However, additional information such as the name of the pesticide and the date of application may appear on the warning sign if it does not detract from the appearance of the sign or change the meaning of the required information. Please note that this issue was considered during the rulemaking process and is addressed in the Response to Comments Document prepared by EPA. (See excerpt from "Worker Protection Standards: A Summary of the Public's Comments and the Agency's Response."). (March 22, 1993)

13-2 Colors of the posting signs

Question: How many different colors on white are required to meet the posting sign requirements? Can red be the only color on a white background?

Answer: White is not necessarily required, although the background color must contrast with red, which is required for the inner circle. Two-colored signs could meet the requirements as long as red were one of the colors. Therefore, red could be the only color on a white background provided the other requirements regarding contrast, legibility, etc. outlined in the rule are met. (March 22, 1993)

13-3 Language requirements on signs

Question: Are the application information provisions of section 170.122 and safety poster information in section 170.135 required to be in a second language?

Answer: No, the application information provisions of section 170.122 and the safety poster information in section 170.135 do not need to be in a second language. Note, however, the EPA produced safety poster will be in English and Spanish. (March 22, 1993)

13-4 Posting signs location requirements

Question: Section 170.122 requires the display of certain information when workers are on an establishment where pesticides have been applied. Does this mean anywhere on the agricultural establishment? Does it apply only to a contiguous property?

Answer: (First question) Yes, whenever workers or handlers employed by the agricultural establishment are anywhere on that establishment, certain information must be displayed.

(Second question) No, it does not necessarily apply only to contiguous property. It applies anytime they are anywhere on the agricultural establishment. (March 22, 1993)

ED_001854_00008312-00031

13-5 Method of display of application information

Question: WPS requires employers to "display" specific information about pesticides for 30 days after their application on the agricultural establishment or the expiration of any Restricted Entry Interval. Does this mean that the information must be displayed like posters, so that all the information is in view at once, or may the information be displayed on sheets of paper that are in a binder or in another convenient manner?

Answer: WPS requires that the information on applications be accessible, legible, and displayed in a central location on the farm, or in the nursery or greenhouse (or in or near a forest, where workers or handlers are likely to congregate or pass by) "where it can be readily seen and read" by workers [40 CFR §§170.122 and 170.135] and handlers [40 CFR §§170.222 and 170.235]. It also requires that workers and handlers be informed of the location and allowed access to it. EPA used the word "display" to indicate that this access must be unrestricted in that it need not be requested. However, any manner of display that meets these criteria is acceptable, including such approaches as page-on-page lists stapled at the top and use of devices such as clipboards or binders. (February 25, 1994)

13-6 Posting after containers have been sold

Question: The regulation at section 170.122 and 170.222 requires posting of information on pesticide applications at a central location for at least 30 days after the expiration of REI (or, if there is no REI, for at least 30 days after the end of the application), or until workers are no longer on the establishment, whichever is earlier. If treated soil is sold (in the pots with the crop) and is moved off the agricultural establishment (i.e., no longer under the control of the agricultural employer), does the application list have to remain posted at the agricultural establishment where pesticide treatment occurred?

Answer: Yes, the application list must be displayed for at least 30 days after the expiration of REI (or, if there is no REI, for at least 30 days after the end of the application), or until workers are no longer on the establishment, whichever is earlier. It is acceptable to note on the list that the treated area (treated plants/soil) is no longer on the agricultural establishment. (February 28, 1995)

13-7 Pesticide application list, harvested crops

Question: If a crop is harvested and sold and the remaining stubble is plowed under, does the application list at the central location still have to contain a listing of applications to that crop? What if another crop is planted in that area within a 30-day period?

Answer: Yes. The list of applications posted at the central location would have to be displayed for at least 30 days after the end of the restricted-entry interval (or, if there is no restricted-entry interval, for at least 30 days after the end of the application) or at least until workers are no longer on the establishment. If another crop is planted within the 30-day period, the list of applications to the previous crop would still have to be displayed as well as any information on pesticide application to the new crop. (February 28, 1995)

13-8 Pesticide application list, non-WPS labeled product

Question: If a grower buys a WPS labeled product and non-WPS labeled product, is he required to list any applications of the non-WPS labeled product on his centrally located information sheet concerning applications of pesticides?

ED_001854_00008312-00032

Answer: No. He is required to list only applications of WPS-labeled products. Nonetheless, the Agency encourages growers to display information on all applications as a matter of providing protection to the workers. (February 28, 1995)

13-9 Posting of private forest land

Question: If a person owns private forest land that the public frequently enters, does he have any responsibility to post this land prior to or after the treatment with a pesticide?

Answer: The fact that the public enters does not trigger the WPS requirement for posting. The WPS does prohibit an agricultural employer from allowing any person to remain in the area during the pesticide application.

In addition, there are specific labeling statements which prohibit the application of the product in such a manner that will contact persons either directly or through drift. Also, there may be non-WPS label specific or additional state or local requirements that are applicable. (March 7, 1995)

13-10 Posting areas with unlimited entry points

Question: If a treated area has unlimited entry points, how often should treated-area warning signs be posted to be "visible from all usual points of entry?" Every 100 feet?

Answer: The rule requires that signs be visible at all usual points of worker entry, including at least each access road, each border with any labor camp adjacent to the treated area, and each footpath and other walking route that enters the treated area. If there are many usual points of entry, then signs must be visible from all usual points of entry. When there are no usual points of worker entry, signs must be posted in the corners of the treated area or a location affording maximum visibility. In areas where there are unlimited points of entry, the agricultural employer must determine the usual points of entry and make signs visible from those points of entry. (March 7, 1995)

13-11 Central posting, large or non-contiguous sites

Question: What is required for central posting when an agricultural establishment is particularly large or has separate workforces on non-contiguous sites?

Answer: The rule requires that certain information (30-day listing of pesticide applications and associated REI's, safety poster, and emergency medical care information) must be displayed in a central location on the agricultural establishment, in a place accessible to workers and handlers. EPA anticipated that there would be one central posting location on the agricultural establishment. However, if because of the size of the establishment or the separate nature of the workforce, there is not one central location that is accessible to all workers, then an employer will need more than one central posting to comply with the accessibility requirement in the rule. By accessible, EPA means that the information must be in a location where it can be readily seen and read and must be unrestricted in that it need not be requested. (March 15, 1995)

13-12 Updating central posting information

Question: Potting soil/plants may be treated with a pesticide in one location and then be moved either during the REI period or during the 30 days after the end of the REI. If they are moved, does the central posting information have to be updated to reflect the current location?

ED_001854_00008312-00033

Answer: To meet the requirement of the regulations, the central posting information must remain reasonably accurate during the 30 days after the REI, or if none, for 30 days after the application, so that a worker will be able to determine which pesticides may be present in areas he will enter. Meeting this performance standard can be accomplished in a number of ways, including: 1) updating the information; or 2) providing the initial information in such a way that it addresses any likely changes to the location of the treated area (the pots); or 3) in addition to providing the initial location of the pesticide application, referring in the posting to markings or to other identifiers on/with the pots that remain with them as they move; or 4) in some other systematic manner that the employer chooses to use to assure that the information remains reasonably accurate. This list of examples is not exhaustive. (March 15, 1995)

13-13 Use of smaller signs

Question: The WPS Rule states that the warning sign shall be at least 14 inches by 16 inches in size, and the letters shall be at least 1 inch in height unless a smaller sign and smaller letters are necessary because the treated area is too small to accommodate a sign of this size. The example provided in the How-to-Comply Manual is when a single potted plant needs posting. Are there other circumstances in which smaller warning signs can be used?

Answer: The intent of the rule is to grant flexibility when a smaller sign would be more appropriate or practical based on spatial limitations of the treated area. For example, the use of the 14 by 16 inch signs may be impractical for individually potted plants, small treated areas on greenhouse benches or in closely spaced plots in nurseries/greenhouses or on farms where crops requiring different treatment regimes are grown in close proximity to one another. In such cases, smaller warning signs are permitted as long as they are readily visible and legible, as one approaches the treated area, and that they are not obscured from view by foliage. It is expected that the smaller warning signs will generally be used in greenhouses and nurseries. The smaller warning signs must conform with all the requirements applicable to the 14 by 16 inch warning sign with the exception of the size requirement. The signs must be of sufficient size and adequate construction to remain visible and legible during the time they are posted. To assure this, all posted warning signs must be constructed in such a way that would prevent them from drooping or wrapping around their supports. Since some States may adopt more restrictive requirements, and not choose to permit the use of smaller warning signs, an employer should check with their State agency responsible for worker protection to verify the State's policy on posting. (June 14, 1996)

14 Scope

14-1 Persons other than workers, and WPS

Question: In several sections reference is made to "...any person" or "persons." Do these apply only to workers or to everyone? (See section 170.110 vs. Table 1 B)

Answer: The language of the rule (170.110(b) and (c)) clearly states that the restrictions on entry associated with applications in nurseries and greenhouses apply to any persons, other than an appropriately trained and equipped handler. This means it applies to non-workers as well as workers. (March 22, 1993)

14-2(a) Prisons, coverage by WPS

Question: Are prisons subject to the requirements of the WPS?

Answer: There is nothing in WPS that exempts prisons from the duty to comply with WPS. WPS protections must be provided to pesticide handlers and agricultural workers any time a pesticide product bearing WPS labeling is used on an agricultural establishment in the commercial or research production of agricultural plants. Whether a

ED_001854_00008312-00034

particular prison meets the definition of an agricultural employer or handler employer or is an agricultural establishment engaged in the commercial or research production of agricultural plants will have to be established on a case-by-case basis, as will whether a prisoner is an agricultural worker or pesticide handler. Factors to be considered include whether the prisoner is receiving any form of compensation and whether the production of agricultural plants is for commercial or research purposes.

Regardless of the determination of whether the prison is an agricultural or handler employer or is an agricultural establishment, EPA encourages that prisoners be afforded the WPS protections. (November 17, 1993)

14-2(b) Prisons, responsibility for providing WPS protections

Question: Who is responsible for assuring WPS protections are provided to prisoners?

Answer: Prison facilities that are agricultural employers or handler employers must provide WPS protections to each prisoner who is an agricultural worker or pesticide handler. The prison must require each person who supervises any prisoner-worker or prisoner-handler to assure that the prisoner-worker or prisoner-handler receives the protections required by WPS. These protections include providing:

- Information at a central location,
- Notice to workers about applications and entry restrictions,
- Instructions to handlers and early-entry workers,
- Pesticide safety training,
- Personal Protective Equipment (including its maintenance),
- Decontamination facilities, and
- Emergency assistance.

When a prisoner is performing tasks as an agricultural worker or pesticide handler on an agricultural establishment that is NOT owned by the prison, the owner of the agricultural establishment also has WPS responsibilities towards the prisoner.

- Prisoner-handlers: When the prisoner is performing handler tasks, the owner of the agricultural establishment must assure that, if the prison is acting as a commercial pesticide handling establishment, the prison is aware of the specific information about applications and entry restrictions on the agricultural establishment. That allows the prison to provide their prisoner-handlers with the information.

- Prisoner-workers: When the prisoner is performing worker tasks, the owner of the agricultural establishment is jointly responsible with the prison (both are agricultural employers) for assuring that the prisoner-workers are provided all of the required WPS protections. This is no different than any agricultural establishment/labor contractor arrangement. (November 17, 1993)

14-3(a) Educational facilities, coverage by WPS

Question: Are educational facilities subject to the requirements of the WPS?

Answer: There is nothing in WPS that exempts educational facilities from the duty to comply with WPS. WPS protections must be provided to pesticide handlers and agricultural workers any time a pesticide product bearing WPS labeling is used on an agricultural establishment in the commercial or research production of agricultural plants. Whether a particular educational facility meets the definition of an agricultural employer or handler employer or is an agricultural establishment engaged in the commercial or research production of agricultural

plants will have to be established on a case-by-case basis, as will whether a student is an agricultural worker or pesticide handler. Factors to be considered include whether the student is receiving any form of compensation and whether the production of agricultural plants is for commercial or research proposes. The Agency intends compensation to be interpreted broadly.

Regardless of the determination of whether the educational institution is an agricultural or handler employer or is an agricultural establishment, EPA encourages that students be afforded the WPS protections. (November 17, 1993)

14-3(b) Educational facilities, responsibility for providing WPS protections

Question: Who is responsible for assuring WPS protections are provided to students?

Answer: Educational facilities that are agricultural employers or handler employers must provide WPS protections to each student who is an agricultural worker or pesticide handler. The educational facility must require each person who supervises any student-worker or student-handler to assure that the student-worker or student-handler receives the protections required by WPS. These protections include providing:

- Information at a central location,
- Notice to workers about applications and entry restrictions,
- Instructions to handlers and early-entry workers,
- Pesticide safety training,
- Personal Protective Equipment (including its maintenance),
- Decontamination facilities, and
- Emergency assistance.

When a student is performing tasks as an agricultural worker or pesticide handler on an agricultural establishment that is NOT owned by the educational facility, the owner of the agricultural establishment also has WPS responsibilities towards the student.

- Student-handlers: When the student is performing handler tasks, the owner of the agricultural establishment must assure that, if the educational facility is acting as a commercial pesticide handling establishment, the educational facility is aware of the specific information about applications and entry restrictions on the agricultural establishment. That allows the educational facility to provide their student-handlers with the information.

- Student-workers: When the student is performing worker tasks, the owner of the agricultural establishment is jointly responsible with the educational facility (both are agricultural employers) for assuring that the student-workers are provided all of the required WPS protections. This is no different than any agricultural establishment/labor contractor arrangement. (November 17, 1993)

14-3(c) Educational facilities, coverage by WPS, compensation

Question: Students participating on academic or research projects may be working as pesticide handlers or agricultural workers. When they receive academic credit for their efforts rather than monetary compensation, are they covered under the WPS?

Answer: The WPS does not define compensation and the Agency intends that compensation should be interpreted very broadly. Stipends or reductions in education costs received as compensation for worker or

ED_001854_00008312-00036

handler tasks performed would be considered compensation. Academic credit alone may be considered compensation in situations where students are engaged in worker or handler activities and for which compensation is normally paid or anticipated. There are also situations where students may be in a treated area when they are not subject to the WPS, such as on a field trip or observing a class demonstration. (November 17, 1993)

14-4 Sod/turf growing establishments

Question: Are agricultural establishments that grow sod/turf for commercial or research purposes included under the WPS?

Answer: Yes, agricultural establishments that grow sod/turf for commercial or research purposes are covered by the WPS.

As defined in 40 CFR part 170.3, agricultural plant means any plant grown or maintained for commercial or research purposes and includes, but is not limited to, food, feed, and fiber plants; trees; turfgrass; flowers, shrubs; ornamentals; and seedlings.

An agricultural establishment growing sod/turf may be a greenhouse, a nursery, or a farm. When sod/turf is grown outdoors, the purpose for which the sod/turf is grown determines whether the agricultural establishment is a nursery or farm. Sod/turf growing establishments are considered to be nurseries if the sod/turf is grown for commercial or research purposes and is to be used in its entirety in another location. Sod/turf growing establishments that are not nurseries and that are growing sod/turf outdoors for commercial or research purposes, for example, for seed production, are considered to be farms. (November 17, 1993)

14-5 Trustee management of an agricultural establishment

Question: Is a bank, or other trustee, that owns, or is responsible for the management of an agricultural establishment, required to comply with the WPS, i.e., is the bank an agricultural employer or handler employer?

Answer: Whether a bank or any other holder of a trust of an agricultural establishment is subject to the requirements of the WPS depends on the degree of control the bank or other trustee exercises over the activities on the agricultural establishment.

Under the WPS, an agricultural employer is defined as "any person who hires, or contracts for, the services of workers, for any type of compensation to perform activities related to the production of agricultural plants, or any person who is an owner of, or is responsible for, the management of an establishment that uses such workers." (40 CFR 170.3)

Under FIFRA, a "person" is defined as any individual, partnership, association, corporation, or any organized group of persons, whether incorporated or not. Therefore, a holder of a trust for an agricultural establishment is considered to be a "person" under FIFRA.

A bank or other holder of a trust may also be considered an "owner" of an agricultural establishment unless the bank or other trustee has both leased the agricultural establishment to another person and granted that person full authority to manage and govern the use of that agricultural establishment.

WPS defines owner as "any person who has a present possessory interest (fee, leasehold, rental, or other) in an agricultural establishment covered by this part. A person who has both leased such agricultural establishment to

ED_001854_00008312-00037

another person and granted that same person the right and full authority to manage and govern the use of such agricultural establishment is not an owner for purposes of this part." (40 CFR 170.3)

A "handler employer" is any employer who is self-employed as a handler or who employs any handler, for any type of compensation. (40 CFR 170.3)

In summary, a bank, or other trustee, that owns or operates an agricultural establishment is considered to be a person under FIFRA, and depending on the degree of control exercised over the activities on an agricultural establishment, could be considered to be a handler employer or agricultural employer for purposes of the WPS. (November 17, 1993)

14-6 Retail establishments, coverage by WPS

Question: Does the WPS cover establishments engaged in the retail sale of plants, including retail nurseries, retail greenhouses, and other commercial establishments in which plants are held for sale?

Answer: Yes, whenever pesticides bearing WPS labeling are employed for WPS-covered uses in such establishments.

EPA addressed this in the record of the WPS rule development. However, there have been some questions about the WPS definitions of greenhouses and nurseries as any "operation engaged in the ... production of agricultural plants." It has been argued that maintenance of a plant for sale is distinct from production and that, therefore, retail operations are not subject to WPS. This is not the position taken by the Agency for purposes of the WPS. In developing the rule, EPA concluded it would not be useful to define production in such a way as to exclude maintenance of plants, whether or not they are being held for sale. In part, this is because such a distinction is difficult to make. For example, while dormant, plants in a "production" orchard are not then growing, while potted plants "held" for retail sale surely are. It was in recognition of this that EPA defined agricultural plants in the WPS as "any plant grown or maintained for commercial or research purposes." In effect, EPA defined production to include maintenance of living plants.

Moreover, when WPS-labeled pesticides are used in such maintenance, the types of worker and handler exposure to them are no different than in non-retail establishments. Therefore, there was no reason to exclude retail establishments on the basis of potential occupational risk. On the other hand, since most purely retail establishments may be expected to hold plants only briefly, pesticide use may be infrequent. In addition, EPA expects that when treatment in such establishments does occur, it will commonly involve pesticides that are unlikely to bear WPS labeling. As a result, EPA expects this question to arise only rarely in practice.

This interpretation is for purposes of the WPS and is not intended to impact other regulations, such as the Certification and Training regulations. (November 17, 1993)

14-7 Agricultural employer, liability when crop is owned by someone other than grower

Question: When a packing house or other purchaser (such as of Christmas trees or citrus) buys a crop from a grower while it is still in the field, or before the crop is planted, or when the packing house contracts to have it grown, and sends its own workers in to harvest it, who has WPS responsibilities toward those harvesters?

Answer: The grower and the packing house management are both agricultural employers under WPS in this situation and therefore have joint responsibility for ensuring compliance with any WPS entry restrictions, training, decontamination or other requirements applicable to the field in which the harvesting takes place. In regard to the liability for individual cases, the Agency will look at the facts of the specific case.

ED_001854_00008312-00038

The WPS definition of agricultural employer is broad because the Agency sought to avoid circumstances in which confusion about responsibility could lead to failures to adequately protect workers. The definition covers BOTH owners/managers of agricultural establishments AND employers of agricultural workers. Thus, in addition to those responsible for the management of the agricultural establishment, the packing house is a responsible agricultural employer in the same way that a labor contractor would be. For further discussion on liability, attached are the following references: 1) "The Worker Protection Standard: A Summary of the Public's Comments and the Agency's Response," section D., "Comments on Definitions;" and 2) "The Worker Protection Standard," page 38135, comment number 8.

Reference Number 1: "The Worker Protection Standard: A Summary of the Public's Comments and the Agency's Response," section D., "Comments on Definitions."

> Employer. In keeping with the use of the employment relationship to assign primary responsibility for protection of agricultural workers in the final rule, a definition of "agricultural employer" has been added to subpart A. This definition is intended to encompass all employers of workers who may be exposed to pesticides while engaged in agricultural-plant activities. The definition of "handler employer" has also been added to subpart A. The definitions are derived from the definition of "employer" in the NPRM.
>
> Persons falling under the definitions of "agricultural employer" are responsible for the requirements of subpart B. In some cases the employer of agricultural workers also will be an employer of workers who handle pesticides ("handler employer") and therefore responsible for the requirement of subpart C (for employer, if the same grower hires both fieldworkers and handlers, or if the same worker is hired to handle pesticides and to perform other agricultural activities.)
>
> The definition of agricultural employer is intended to include persons who have (1) a position of ownership, management or control within an agricultural establishment, i.e. a farm, forest, nursery or greenhouse; or (2) an employment relationship to agricultural workers. The relevant positions of control identified in the definition include ownership of the establishment (e.g., a farm owner); management of the operation (e.g., a farm operator); and recruiting or furnishing workers for the operation (e.g., a labor contractor).

Reference 2: "The Worker Protection Standard," page 38135, comment number 8.

> Comment # 8: Making agricultural producers responsible for employees' own safety actions is unrealistic.
>
> Response: While compliance is primarily a duty of employers under the final rule, enforcement officials have authority to consider the facts of the case before making a determination of whether a violation has occurred. The Agency agrees, for example, that it would be unfair for employers who expend considerable efforts to assure compliance to be treated in the same manner as less conscientious employers who tolerate encourage noncompliance. However, the Agency believes that it is more appropriate not to intrude by regulation into this area. Enforcement officials have traditionally based their compliance decisions on the facts of an individual case. (November 17, 1993)

14-8 Seed treatments

Question: Are pesticide applications to seed, i.e., seed treatments, covered by the WPS?

Answer: If a product has a WPS reference Statement, and the seed is being treated at an agricultural establishment at or immediately before planting (such as through use of hopper boxes, planter boxes, slurry boxes, or tractor-mounted treaters), WPS applies. If any of these criteria are not met, WPS does not apply. (February 28, 1995)

ED_001854_00008312-00039

14-9 Plants grown for research

Question: Does the worker protection rule apply to pesticides used in conjunction with research (relating to the exemption listed in Subpart B, section 170.102(b)(3)? For example, a greenhouse may conduct plant research and may use pesticides, but not to study the effects of pesticides on plants. Would this situation require compliance with the provisions of the Standard?

Answer: Yes. The WPS must be complied with in the situation outlined above. The WPS applies to plants grown for research purposes, and it does not matter whether the research is to study the effects of pesticides on plants or for some other purpose. WPS protections must be provided to pesticide handlers and agricultural workers any time a pesticide product bearing WPS labeling is used on an agricultural establishment engaged in the commercial or research production of agricultural plants. (February 28, 1995)

14-10 Contracts, liability

Question: If an employer covered by the WPS contracts out spraying on national forest land, does he eliminate his liability if he writes language into his contracts that requires the contractor to comply with the requirements for forestry workers and handlers in 40 CFR Part 170?

Answer: No. An employer may not contract away liability. In the event of a violation of the requirements of the WPS, the Agency would weigh the facts of the case to determine who was responsible for the violations and charge the responsible party or parties with the violation. (February 28, 1995)

14-11 Planting treated seed

Question: Does Part 170 of the Worker Protection Standard apply to areas in which treated seed is being applied or has been applied if the pesticide label does not specify a restricted entry interval?

Answer: For the purposes of the WPS, planting treated seed is not considered a pesticide application and does not trigger WPS handler or worker protections. If, however, seed is treated with a pesticide on an agricultural establishment at or immediately before planting, the WPS applies. See other seed treatment questions and answers. (February 28, 1995)

14-12 Potting soil mixtures, applicability

Question: Greenhouse and nursery growers often order potting soil mixed to their specifications from firms who operate this type of business. The grower may also request that a fungicide or insecticide be included in the potting mix. The potting mixture may be delivered to the grower on the same day that it is made up and the grower could have workers planting seeds or plants in the mixture on the same day. Does the WPS apply to this situation?

Answer: No. The Worker Protection Standard (WPS) does not apply to a product that is not applied on the agricultural establishment in the production of an agricultural plant. However, there may be other labeling provisions that are not specific to WPS that apply. Potting soil treated on a non-agricultural establishment or by a farm, nursery, greenhouse or forest is subject to the labeling provisions of the pesticide product used to treat the soil. Therefore, any label specific non-WPS restricted entry interval (REI) or other labeling restrictions must be met. (February 28, 1995)

ED_001854_00008312-00040

14-13 Potting soil mixtures, requirements to meet

Question: Growers make their own potting mixtures, which include registered fungicides or insecticides. The potting mix may be used over a period of several days. What requirements must the agricultural employer meet? Will there be any kind of restricted entry interval before the soil can be handled by persons who will plant seeds or plants?

Answer: The WPS does apply when potting soil is treated with a pesticide product on an agricultural establishment and that potting soil is used on that agricultural establishment in the production of an agricultural plant as defined in the WPS.

In this case, the treated potting mix is the treated area, and the REI would apply to the potting mix. The REI would begin when the application is completed.

Mechanical filling of pots or mechanical planting of seeds or plants may take place prior to the expiration of the restricted entry interval; however, workers may not come into contact with the treated soil unless they meet the exceptions as provided for in the WPS Rule. (February 28, 1995)

14-14 Conservation Reserve Program land, coverage by WPS

Question: Do WPS requirements apply to pesticide use on Conservation Reserve Program (CRP) land, land originally used for agriculture but taken out of production?

Answer: If the land is not used in the production of an agricultural plant, for research or commercial purposes, the WPS does not apply. CRP plantings that are not expected to be harvested would be expected to fall outside the scope of WPS. Any pesticide applications made in preparation for planting an agricultural plant or to an agricultural plant that is intended to be harvested will be subject to the WPS regulation. (February 28, 1995)

14-15 Volunteers, coverage by WPS

Question: If members of a garden club volunteer their services in the production of flowers and plants that are sold at the club's annual fund raiser, and pesticides are used, is the volunteer a worker under the Rule?

Answer: A volunteer is not considered a worker under the definition in 40 CFR part 170.3 unless they receive some form of compensation. Regardless of whether compensation is provided, the Agency encourages that volunteers be afforded the WPS protections. (February 28, 1995)

14-16 Workers hired over 30 days after application

Question: If an agricultural employer hires workers to perform hand tasks in fields that were treated more than 33 days previously, does he need to train them or provide them with a decontamination site?

Answer: No, he does not have to provide either if no worker enters an area to which a pesticide has been applied or for which no REI has been in effect within the last 30 days. (March 7, 1995)

14-17 Persons stepping up nursery stock

Question: Will the person stepping up the stock (e.g. repotting) to 3 gallon containers from 1 gallon containers be considered a nurserymen under WPS?

Answer: The WPS does not use the term nurserymen in terms of its applicability; the WPS would apply to nurserymen if they meet the definition of either workers, handlers, agricultural employers, or handler employers. Persons stepping up stock (repotting) without applying a pesticide are workers. (March 7, 1995)

14-18 Are grower cooperatives establishments

Question: Are grower cooperatives considered an establishment under the Rule?

Answer: It depends on the activities of the cooperative. The cooperative may be an agricultural establishment or a commercial pesticide handling establishment, if it meets the definition in the regulation. The cooperative may also be an agricultural employer or handler employer. (March 7, 1995)

14-19 Persons carrying nursery stock

Question: Under the definition of nursery, is the person that carries nursery stock included in the nursery portion of this rule?

Answer: Yes. The person that carries nursery stock is considered a worker if he is employed by the agricultural establishment. Carrying plants is a worker task. (March 7, 1995)

14-20 Persons selling produce from home gardens

Question: Are persons who grow and sell produce from their home gardens covered by the WPS?

Answer: Yes, such persons are covered by the WPS if they use a pesticide with the WPS statement on the label in the production of the produce being sold. The exception for home gardens does not apply when the produce is produced for commercial purposes.

Note, if the person does not employ workers or handlers and only he or his immediate family as defined in the rule are performing the work, only certain requirements apply. (See question 7.17 of IGW Q & A Document.) (March 7, 1995)

14-21 Employees of landfills

Question: Employees of sanitary landfills that accept pesticide containers can come in contact with pesticides remaining in the containers. Are these employers covered by the WPS?

Answer: No, sanitary landfills are not covered under the WPS. (March 7, 1995)

14-22 Garden clubs, coverage by WPS

Question: Is the garden club considered an agricultural employer?

Answer: Yes. The garden club is an agricultural employer if (1) it hires or contracts for the services of workers, for any type of compensation, to perform activities related to the production of agricultural plants; or (2) if it is an owner of or is responsible for the management or condition of an agricultural establishment that uses such workers.

ED_001854_00008312-00042

However, the garden club is not an agricultural employer if the only persons working in the garden club in production of agricultural plants are uncompensated volunteers. (March 7, 1995)

14-23 Workers not involved in production of agricultural plants, coverage by WPS

Question: Are employees of an agriculture establishment but whose work is not directly involved in the production of agricultural plants, covered by the WPS?

Answer: No, they are not covered as workers or handlers. Examples of employees not normally considered agriculture workers or handlers under WPS would include but not limited to office employees, truck drivers, mechanics, road workers, surveyors and any other workers not engaged in worker/handler activities. However, note that some provisions of the WPS require protections for persons other than workers and handlers. Some requirements apply to all persons some apply to persons engaged in repairing, cleaning or adjusting application equipment or those who clean or launder pesticide contaminated PPE. Please refer to Section 170.110, 170.234, and 170.240 for further information. (March 7, 1995)

14-24 Production of agricultural plants for other than direct sale

Question: What is the scope of the WPS with respect to establishments producing agricultural plants for other than direct sale, i.e., in-house use?

Answer: There is no exception for agricultural plants produced for other than direct sale, i.e., in-house use. The WPS covers an agricultural establishment if (1) a WPS-labeled agricultural pesticide is used on the establishment, (2) workers or handlers are employed by or on the agricultural establishment, (3) the establishment is a farm, forest, nursery, or greenhouse, as defined in the WPS, and (4) the establishment or the activity is not covered by one of the exceptions specifically described in the rule, Section 170.102 (b).

For instance, the following operations are covered by the WPS: Production of hay or feed grown for livestock on dairy farms, cattle ranches, or other livestock operations; sod farms, greenhouses, or nurseries operated by golf courses; and greenhouses and nurseries operated by theme parks, hotel chains, botanical gardens, and state and local governments. (Note: Pasture and rangeland used for grazing are excluded.) (March 15, 1995)

14-25 Employees working for a packing shed, coverage by WPS

Question: Are employees working for a packing shed covered by the WPS?

Answer: It depends on the activity and where it occurs. If employees are packing produce into containers in the field, they are covered by the WPS. If employees are working in a packing shed after harvest, they are not covered. (Section 170.102(b)(9) and 170.202(b)(8). See also questions and answers 4.12 and 14.17 for definitions of when an agricultural plant is considered "harvested.") (June 14, 1996)

14-26 Day haulers, coverage by WPS

Question: Must day haulers -- an operation that transports workers to the agricultural establishment -- comply with the WPS, i.e., are day haulers agricultural employers?

Answer: The WPS defines agricultural employers as "any person who hires or contracts for the services of workers, for any type of compensation, to perform activities related to the production of agricultural plants, or any person who is an owner or is responsible for the management or condition of an agricultural establishment

ED_001854_00008312-00043

that uses such workers." Day haulers who hire or contract for the services of workers in the field, or who are acting for someone who is doing this, would be considered agricultural employers and must comply with the WPS. If a person only provides transportation to and from the agricultural establishment, then he would not be covered by the WPS. (June 14, 1996)

14-27 Are researchers considered workers or handlers?

Question: Agricultural research involving pesticides may often necessitate researchers and research assistants to enter pesticide treated areas before applicable REIs have expired to collect data and/or samples for analysis. Given that research uses of registered pesticides (i.e., use according to the label) are covered under the WPS, would researchers entering treated areas before the expiration of the REI be considered workers or handlers?

Answer: It depends on the activity the researcher is performing. If he/she is applying a pesticide or performing other handler activities, he/she is a handler. If he/she performs worker activities, he/she is a worker. A person who is entering the treated area during the REI to collect data and/or samples related to assessing pest numbers or damage, pesticide distribution, or the status or requirements of agricultural plants and is not performing any other hand labor tasks is considered a crop advisor under the rule. Crop advisors are considered handlers during the application and until the expiration of the REI, at which time they are considered workers in terms of coverage under the WPS. For additional information about crop advisor requirements, please see FR Notice Volume 60 No. 85 May 3, 1995, page 21928 [40 CFR part 170].
(June 14, 1996)

14-28 Field transplant operations, coverage by WPS

Question: Several field agricultural crops are grown using transplants from nursery seedbeds. Most current agricultural practice involves the transplants being set into the ground concurrent with an at-plant pesticide application. Such transplant operations usually are accomplished using the following two methods: (1) manual transplanting with concurrent pesticide application where the employees plant the seedlings in advance of the spray-rig, with the spray-rig following behind applying the pesticide; or (2) mechanical transplant/application process where equipment is a combination planting apparatus and spray-rig on which employee(s) sit and feed seedlings into the planting arm or wheel (depending on the equipment) which mechanically sets plants into ground while at the same time a pesticide is applied. Additionally, there may be an employee following the rig to assure that the planter/spray-rig is operating and setting the plants in properly. NOTE: There are several variations of these transplant type operations where planting occurs at the same time as pesticide applications (dip solutions, etc.). How will these transplant operations be treated under the WPS?

Answer: Under the WPS, agricultural employers may not allow any person (including workers), other than an appropriately trained and equipped handler, to enter or remain in the treated area during an application. Further, employers and pesticide handlers must assure that no pesticide is applied so as to contact, either directly or through drift, any worker or other person, other than an appropriately trained and equipped handler.

For field transplant operations such as those described in number one above (1), the employees are considered workers since they are solely performing hand-labor tasks as transplanters and are not involved in the pesticide application itself. As such, they may not enter or remain in a treated area during the application of a pesticide. If the workers can keep in front of the treated area (that area to where the pesticide is being directed or has been directed) and the employer and handler assure that the workers do not come into contact with the pesticide or pesticide treated surfaces while transplanting (directly or through drift), then the operation would not constitute a WPS violation. It is the employer's responsibility to notify the workers of the pesticide application and to assure that the workers who are transplanting seedlings constantly remain in front or outside of the treated area.

ED_001854_00008312-00044

For field transplant operations that occur concurrently with pesticide application such as those described in number two above (2), and for similar pesticide applications combined with another agricultural operation which may require additional employees to operate the supplemental equipment (at-plant seed treatments, etc.), the Agency views the entire operation to be part of a "pesticide application process." Therefore, the employees will be considered handlers and are not subject to restrictions associated with remaining outside of the treated area. However, all employees taking part in such a transplant operation must be trained and equipped as handlers, including those following the rig as described in the question above. These employees may not perform tasks in the treated area other than those described above or otherwise allowed by the regulation.

NOTE: In addition, it is the employer's responsibility to comply with other applicable rules and provisions, e.g., the notification requirements and nurseries.
(June 14, 1996)

15 Training

15-1 Training verification card

Question: How will growers or labor contractors know if their workers have been trained if documentation is not required?

Answer: The employer must make sure the worker receives training if he/she is not sure the worker has been trained already. However, no documentation of training by the worker is required by the Standard. To assist the employer in verifying whether the training has occurred, EPA is defining a voluntary training verification system which may incorporate the issuance of a card upon completion of training. (March 22, 1993)

15-2 Exceptions to training requirements

Question: Section 170.130(a)(3)(ii) allows for an interim (five year) exception to worker training. Does this mean that if entering a treated property for less than 16 days that no training is required? If entering several different establishments every day to conduct hand labor activities, must the worker receive training for <u>each</u> field?

Answer: (First question) Until October 20, 1997, workers must be trained before they accumulate more than 15 separate days of entry into treated areas on a single agricultural establishment where within the past 30 days, a pesticide has been applied or a restricted-entry interval imposed by the label has been in effect. The accumulation of the 15 days accrues independently at each establishment. These 15 days need not be consecutive and may occur over several periods of employment or over several seasons or years.

(Second question) No, once a worker has received training, the worker need not be retrained for 5 years, but each employer must assure that the worker has been trained. (March 22, 1993)

15-3 Issuance of training verification cards

Question: Who will approve/issue the EPA Worker Protection Standard Certificate?

Answer: The training verification program, which will include use of a training verification card, is being developed by EPA with participation by representatives from the Regions, States, training experts, worker advocacy groups, industry groups and grower groups. The details of the training verification program will be announced in the future. The issue of who will approve/issue the EPA Worker Protection Standard verification card will be addressed at that time. (March 22, 1993)

ED_001854_00008312-00045

15-4 Additional training for certified applicators

Question: According to the Rule, if an employer hires workers or handlers who are certified applicators under Part 171, he is not required to provide them with pesticide safety training. Is the employer required to provide them with training on subjects he knows were not included in their certification training (e.g., heat-related illness and the WPS)?

Answer: No. The handler employer or agricultural employer is not required to provide pesticide safety training to workers or handlers who are certified applicators for areas he knows were not covered during the certified applicator training. (February 28, 1995)

15-5 40 CFR section 170.234(c)(2,3); do requirements herein constitute a training program?

Question: Are the requirements in section 170.234(c)(2,3) considered a training program and could compliance be accomplished with a brief demonstration and a statement that pesticides can be hazardous? Is this provision contradicting the WPS definition of handlers?

Answer: No, the requirements under the above section are not considered a training program. Compliance would be accomplished by following section 170.234 (c)(1,2,3). Specifically, before allowing any other person besides a handler to repair the equipment, the handler employer must remove pesticide residues. If removal is not feasible, the employer must inform the repairman that the equipment is contaminated, that pesticide exposure has the potential to produce harmful effects, and about the correct way to handle the contaminated equipment.

This provision does not contradict the definition of handler because handlers, unlike outside repairmen, are employed by an agricultural establishment or commercial pesticide handling establishment. For pesticide handlers repairing, cleaning, or adjusting equipment, the employer has to instruct the handler in the safe operation of equipment for mixing, loading, transferring, or applying pesticide, including, when relevant, chemigation safety and drift avoidance. (June 14, 1996)

16 Enforcement and Liability

16-1 Guidance to States; determining recipient of WPS enforcement actions

Question: What guidance has EPA provided the States regarding determining the appropriate recipients of WPS enforcement actions?

Answer: EPA issued guidance on February 13, 1995, entitled "Summary Guidance on Issuance of WPS Enforcement Actions". In that document, EPA recommended that a common sense, case-by-case approach be used in determining the appropriate recipient(s) of a WPS enforcement action. To provide further clarification and assistance in determining the appropriate recipients, the Agency recommended that State Lead Agencies consider the following ten (10) factors:

(1) Who has control over pesticide use;
(2) Who directs pesticide use;
(3) Who has control over the agricultural establishment for posting and other WPS-related responsibilities;
(4) Who gives direction on the agricultural establishment for posting and other WPS-related responsibilities;
(5) Who has control over the practices used by agricultural workers on the establishment;
(6) Who directs the practices used by agricultural workers on the establishment;
(7) Measures taken to comply with provisions of the WPS;

ED_001854_00008312-00046

(8) Actions taken in response to incidents of noncompliance;
(9) History of prior violations; and
(10) Ability to assure continuing compliance with the WPS.
(June 14, 1996)

16-2 Responsibility for agricultural workers brought in by labor contractor

Question: Who has the responsibility for training crews of agricultural workers brought in by a labor contractor?

Answer: The agricultural establishment owner, operators and employers, including labor contractors, are jointly responsible for providing training and other WPS protections to workers, and for ensuring compliance with WPS requirements. The agricultural owner, operator and employer, including labor contractors, each may be liable for a given WPS violation. During WPS implementation, EPA recommends that a common sense, case-by-case approach be used in determining the appropriate recipient(s) of a WPS enforcement action as referenced in question 16.11. Documentation by agricultural owners/operators/employers could assist them in demonstrating to State regulatory officials their efforts to comply and their responses to instances of noncompliance. (June 14, 1996)

16-3 Employer responsibility for compliance in chain of command

Question: The WPS holds agricultural owners, operators and employers responsible for compliance. How far up a chain of command does this responsibility go? Do crew leaders and farm managers include professors supervising research studies and issuing grades? Does employer responsibility for compliance extend to administrators, including experimental station directors, department chairpersons, agriculture college deans, university chancellors, presidents and boards of curators?

Answer: The WPS, at section 170.3, defines agricultural employer as any person who hires or contracts for the services of workers, for any type of compensation, to perform activities related to the production of agricultural plants, or any person who is an owner of or is responsible for the management or condition of an agricultural establishment that uses such workers. Thus, any person meeting this definition must assure that workers are provided WPS protections and may be liable in the event protections are not provided. The Agency identified 10 factors to guide the States in determining the appropriate recipient(s) of an enforcement action as referenced in question 16.11. (June 14, 1996)

16-4 Employer liability under WPS if workers claim not to have been trained in some WPS requirements

Question: If an agricultural employer's workers are trained by a trainer who meets the criteria in the WPS at section 170.130(c)(2), will the employer be liable under WPS if workers claim not to have been trained in some part of WPS requirements? Is fifteen minutes of worker training sufficient to protect against litigation?

Answer: The employer would not be liable for WPS training violations if the training meets the requirements of the WPS at section 170.130. The adequacy of worker training is determined by the factors set out in section 170.130(c)(4). EPA cannot address civil liability. No specific time limit is established by the rule; the contents of the training must include the requirements in section 170.130.
(June 14, 1996)

ED_001854_00008312-00047

17 Activities Covered by the WPS

17-1 Activities related to the production of agricultural plants

Question: Section 170.3 defines a "worker," in part, as any person who is "performing activities relating to the production of agricultural plants." For the purposes of determining whether an employee meets the definition of a "worker" under the WPS (and would therefore be covered by the WPS), what types of activities would be considered to be "activities relating to the production of agricultural plants?"

Answer: For the purposes of the WPS, activities that are considered to be "activities related to the production of agricultural plants" are those tasks that are directly related to cultivation and/or production of the agricultural plants or the "crop." Such tasks include (but are not necessarily limited to): soil and seedbed preparation; seeding; planting; moving plants, containers and nursery/greenhouse stock; transplanting; weeding; fertilizing; mulching; raking; pruning, thinning, harvesting and any other hand labor activities as defined in the WPS; irrigation and activities related to preparing for irrigation; and other miscellaneous non-handler tasks involved with protecting and/or improving production of the commodity (operating fans and heaters for greenhouses, frost/freeze protection activities, staking, etc.) (March 26, 2004)

17-2 Employees not performing worker or handler tasks

Question: Are employees of an agricultural establishment (including contract labor) covered by the WPS if they are employed by the establishment but do not meet the WPS definition of workers or handers because they are not performing worker or handler activities/tasks? What are some examples of employees that may work on an agricultural establishment, but would not be covered by the WPS as workers or handlers?

Answer: No, employees of an agricultural establishment (including contract labor) that are not performing worker or handler tasks are not covered by the WPS. **[NOTE**: During a WPS covered pesticide application on a WPS covered establishment, certain provisions of the WPS apply to all persons, not just workers and handlers. There are also WPS requirements that apply to persons engaged in repairing, cleaning or adjusting application equipment, and to persons who clean or launder pesticide contaminated PPE. Please refer to Sections 170.110, 170.210, 170.234, and 170.240 for further information. Examples of employees that would not normally be considered workers or handlers under the WPS would include (but are not necessarily limited to): office employees; retail sales staff; building and construction crews; building maintenance/cleaning crews; food preparation or food service staff; truck drivers and/or haulers; mechanics; road workers; surveyors; power line crews; and any other employees not engaged in WPS defined worker/handler activities. (March 26, 2004)

17-3 Is road construction in forests an activity related to the production of an agricultural plant?

Question: In forest operations, rudimentary road construction must often take place to allow harvesting of the timber. This entails laying gravel onto cleared paths so trucks and harvest crews have access to forest areas being harvested. Assuming a WPS covered product has been applied to the forest, would the construction of the road in this situation be considered an activity related to the production of an agricultural plant (timber), such that the landowner and/or the road construction company must provide WPS protections for the road construction crew because they meet the definition of agricultural workers?

Answer: No, the construction of the road would not be considered an activity directly related to the production of an agricultural plant (timber in this case). Hence, the road construction crew would not be considered agricultural workers under the WPS, and the landowner and/or the road construction company would not need to provide general WPS protections for the road construction crew. However, please note that during the application of a

covered pesticide on a covered establishment, certain WPS provisions apply to all persons, not just workers and handlers. Please refer to Sections 170.110 and 170.210. Also see question 14-23 for further guidance and clarification. (March 26, 2004)

17-4 Is harvesting pine straw in a forest covered by the WPS?

Question: In pine forest operations, the main "crop" is the lumber from the pine forest, but pine straw is often collected from the forest floor as a byproduct. In many cases, a herbicide is applied to the forest floor for the purpose of destroying vines/weeds because they may complicate harvesting and baling of the pine straw, or because the vines/weeds are considered an invasive species that would contaminate the straw and complicated movement of the harvested pine straw due to varying State quarantine laws. Does this activity or production practice fall under the scope of the WPS? If so, please explain EPA's rationale for this determination, and explain how the different aspects of this practice should be treated under WPS.

Answer: Yes, this activity/production practice does fall under the scope of the WPS. Under the WPS, a forest is defined as any operation engaged in the outdoor production of any agricultural plant to produce wood fiber or timber products. A pine forest operation is covered under the WPS as a forest since the pine trees are agricultural plants being grown for commercial purposes to produce wood fiber or timber products. The pine trees are the agricultural plants in this case, and the lumber and the pine straw would both be considered "timber products." Activities related to raising the pine trees and managing the overall forest operation to obtain the eventual timber products would be considered activities related to the production of agricultural plants. Therefore, herbicide applications to the forest floor to facilitate harvesting of pine straw or to allow shipment of the pine straw under State quarantine laws, would be covered under the WPS (assuming the herbicide is a WPS labeled product). Even though the pine straw may be considered a byproduct or secondary product compared to the actual lumber, it is still a timber product produced from a forest operation covered under the WPS.

Collection of the pine straw would be considered harvesting and a worker activity under the WPS. If the collection of the pine straw was accomplished through the use of mechanized equipment, then the harvesting would not necessarily be considered "hand labor" if there was negligible contact with the pine straw during the process. The pine straw would not be considered to be harvested until it was baled and/or otherwise removed from the forest floor, so herbicide applications to the forest floor while the pine straw was still present would not be considered a post-harvest application and would not be excepted from the WPS. [This situation would be similar to the collection of fallen nuts from an orchard floor. Herbicide applications to the orchard floor to kill weeds in order to facilitate collection of the nuts would be a covered pesticide application. Collection of the nuts would be considered harvesting, and the nuts would not be considered to be harvested until they were either packed into containers or collection bins or otherwise removed from the orchard.] (March 26, 2004)

Message

From: Strauss, Linda [Strauss.Linda@epa.gov]
Sent: 6/9/2017 2:14:42 PM
To: Cleland-Hamnett, Wendy [Cleland-Hamnett.Wendy@epa.gov]; Wise, Louise [Wise.Louise@epa.gov]; Beck, Nancy [Beck.Nancy@epa.gov]
CC: Dunton, Cheryl [Dunton.Cheryl@epa.gov]; Jakob, Avivah [Jakob.Avivah@epa.gov]
Subject: Hispanic Communications Network Spanish-language PSA scripts and web
Attachments: HCN WPS audio script - 2 buddies talking.docx; HCN WPS audio script - couple talking.docx; HCN WPS audio script - father son talking.docx; HCN-WPS wepg Sp 6.7.17.pdf; HCN-WPS webpg Sp-Engl 6.7.17.pdf

Deliberative Process / Ex. 5 **Regarding HCN's web, they will ONLY be posting in Spanish – the last attachment has the rough translation; PSAs will be on there.**

Is this OK to go?

Linda

From: Keigwin, Richard
Sent: Thursday, June 01, 2017 10:49 PM
To: Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Cleland-Hamnett, Wendy <Cleland-Hamnett.Wendy@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>; Dunton, Cheryl <Dunton.Cheryl@epa.gov>; Jakob, Avivah <Jakob.Avivah@epa.gov>
Subject: Re: WPS audio PSAs and HCN webpage info

Deliberative Process / Ex. 5

Rick Keigwin
Acting Director, Office of Pesticide Programs
U.S. Environmental Protection Agency

Sent from my iPhone

On Jun 1, 2017, at 1:05 PM, Strauss, Linda <Strauss.Linda@epa.gov> wrote:

Rick -- OPP is in the process of making your changes (highlighted below in yellow).

Wendy, Nancy, Louise – Heads up - OPP needs approval of this webpage by June 9th to be able to meet the schedule to air three audio PSAs the week of June 12th.

Any issues moving forward? Script 1 talks about the WPS update and script 5 talks about revised protections. These give good basic information on ways farmworkers can protect themselves from pesticides in a way they can understand and relate to.

OPP has contracted with the Hispanic Communications Network (HCN) to inform farm workers and pesticide handlers about how to protect themselves from pesticide illness or injury and to bring awareness of the agricultural Worker Protection Standard (WPS). The campaign focuses only on the core safety messages that remain constant in the old and new regulations. These core safety messages are the steps workers/handlers can take to protect themselves from pesticide illness or injury.

OPP and HCN developed six short audio PSAs in Spanish. The scripts and recordings were approved by OPA/Ron Slotkin via PROTRAC on 5/9/17. The Spanish scripts and English translations are attached for reference.

Three of the PSAs are scheduled to air on HCN's affiliate radio stations the week of June 12th. The remaining three PSAs are scheduled to air in July.

In addition to airing these PSAs on the radio, HCN has developed a Spanish-language webpage on the WPS for our review and approval. The webpage provides general information on the WPS/pesticide safety and links to the three PSAs that are scheduled to air in June. Attached is the webpage HCN developed as well as its English translation. Note that the English translation is not exact, therefore it is important not to correct or change words or sentences, but to comment on the concepts themselves.

L

From: Keigwin, Richard
Sent: Wednesday, May 31, 2017 9:57 AM
To: Sisco, Debby <Sisco.Debby@epa.gov>; Gesalman, Claire <Gesalman.Claire@epa.gov>
Cc: Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Berckes, Nicole <Berckes.Nicole@epa.gov>
Subject: RE: Hispanic Communications Network Spanish-language webpage on WPS NEEDS QUICK TURN-AROUND

As I mentioned yesterday, I didn't receive this for review on Friday. Deliberative Process / Ex. 5

Deliberative Process / Ex. 5

HISPANIC
COMMUNICATIONS·NETWORK

TWO BUDDIES TALKING

Client: EPA	**Client Approval:**
Campaign: WORKER PROTECTION STANDARD	**Production Date:**
Shipment Date:	**Flight Date:**
Title: El Hábito de Cambiarse la Ropa (The habit of changing your clothes)	**Notes/Length:**

English or SFX/Direction	**Spanish Text Script**
Story telling approach. The characters can also be switched to females.	*(LOS DOS PERSONAJES PUEDEN SER, INDISTINTAMENTE HOMBRE O MUJER)*
You hear an announcement that indicates the end of the working day JUAN: (With a mischievous tone) Buddy, it's time to take off your clothes. JOSÉ: (In a tone of disbelief) What's going on, buddy? ANNOUNCER: No, it's not a joke. If you work in the field or handle pesticides, at the end of the working day it is necessary to change all your clothes - trousers, shirt, scarves, caps and shoes. The pesticides that are on plants and in the dirt can stick to your clothes and shoes. JUAN: I learned during training not to go near my family or enter the house until I've changed out of my work clothes. JOSE: That's good advice buddy! ANNOUNCER: That's right. Don't take risks. Work clothes should also be washed separately from the	*Se escucha un aviso que indica el fin de la jornada laboral* JUAN: (Con tono pícaro) Compadre, llegó la hora de quitarse la ropa... JOSÉ: (Con tono de incredulidad) ¿Qué pasó compadre? LOCUTORA: No, no es broma. Si trabajas en el campo o manejas pesticidas, al final de la jornada laboral es **necesario** cambiarse **toda** la ropa, pantalón, camisa, pañuelos, gorras y zapatos. Los pesticidas que están en las plantas y en la tierra se pueden pegar a la ropa y a los zapatos. JUAN: Aprendí en un entrenamiento que no me debo acercar a la familia o entrar a la casa hasta que no me haya cambiado la ropa de trabajo. JOSÉ: !Qué buen consejo compadre! LOCUTORA: Así es. No corras riesgos. La ropa de trabajo debe también lavarse separadamente de la

HISPANIC
COMMUNICATIONS•NETWORK

household laundry and it is necessary to wash and bathe before eating, drinking, using your cell phone and even chewing gum. ANNOUNCER: Better safe than sorry ... For more information in Spanish on the Worker Protection Standard and the important changes for farmworkers and pesticide handlers, visit laredhispana.org. Tagline: A message from this station, the United States Environmental Protection Agency and laredhispana.org.	ropa de familia y es necesario asearse y bañarse antes de comer, beber, usar el teléfono celular y hasta mascar chicle. LOCUTOR: Más vale prevenir que lamentar... Para más información en español sobre el Estándar para la Protección del Trabajador y los cambios importantes para los trabajadores agrícolas y manipuladores de pesticidas visita laredhispana.org. Tagline: Un mensaje de esta estación, la Agencia de Protección Ambiental de Estados Unidos y laredhispana.org.

HISPANIC COMMUNICATIONS NETWORK

COUPLE TALKING

Client: EPA	**Client Approval:**
Campaign: WORKER PROTECTION STANDARD	**Production Date:**
Shipment Date:	**Flight Date:**
Title: Llegando a Casa (Arriving home)	**Notes/Length:**

English or SFX/Direction	**Spanish Text Script**
Theme: Understand there are health risks of from pesticide exposure	
HUSBAND: "Home sweet home" WIFE: My love… come here, I'm dying for a kiss... HUSBAND: No do not come one step further, don't come near me. WIFE: Are you mad at me? HUSBAND: On the contrary, it's because I love you. WIFE: I don't understand a THING. HUSBAND: Today I took a safety-training course for farmworkers and handlers who use pesticides or work in areas where pesticides have been applied. When I get home, I have to separate my work clothes from my other clothes, give myself a good bath with lots of soap and water, put on clean clothes, and then ... All the hugs and kisses you want. WIFE: That's why I love you so much, you always take care of us… like the saying goes, better safe than sorry. ANNOUNCER: If you work with or near pesticides it's important to understand pesticide exposure and how to prevent the risk of you or your family getting sick. Learn about the worker protection standard for	ESPOSO: "Hogar Dulce Hogar!" ESPOSA: Mi amor…. Venga que me muero por darle un beso... ESPOSO: Ni un paso, no te me acerques. ESPOSA: ¿Vienes enojado cariño?... ESPOSO: Por el contrario, porque te amo, es que no lo hago. ESPOSA: No entiendo NADA. ESPOSO: Hoy tomé un curso de capacitación de seguridad para los trabajadores agrícolas y manipuladores de pesticidas quienes trabajamos en las áreas donde han sido aplicados los pesticidas. Al llegar a casa, tengo que separar mi ropa de trabajo de mi otra ropa, darme un buen baño con mucha agua y jabón, ponerme ropa limpia y después… Todos los abrazos y besos que quieras. ESPOSA: Por eso te quiero, siempre nos cuidas… porque como dice el dicho, mas vale prevenir que lamentar. LOCUTOR: Si trabajas con pesticidas o cerca de ellos, es importante saber cómo prevenir el riesgo del

HISPANIC
COMMUNICATIONS NETWORK

farmworkers at laredhispana.org. Tagline: A message from this station, the United States Environmental Protection Agency and laredhispana.org.	enfermo a ti y a tu familia. Infórmate sobre las reglas de protección a los trabajadores del campo en laredhispana.org. Tagline: Un mensaje de esta estación, la Agencia de Protección Ambiental de Estados Unidos y laredhispana.org.

HISPANIC
COMMUNICATIONS·NETWORK

FATHER – SON TALKING

Client: EPA	**Client Approval:**
Campaign: WORKER PROTECTION STANDARD	**Production Date:**
Shipment Date:	**Flight Date:**
Working Title: Oye Papá (Listen to me, Dad)	**Notes/Length:**

English or SFX/Direction	Spanish Text Script
Theme: Understand where pesticides are found	
SON: Hey Dad, since you work in the field did you know about pesticides and that there many kinds of pesticides? DAD: Really? Where did you learn that? At school? SON: Yes, the teacher taught us that there are protections for field workers, like you... *(with a playful/smile tone)* DAD: And, what did you learn? SON: Pesticides are everywhere. On plants, the ground, on produce, and clothes too. That is why you have to take off your work clothes and wash thoroughly before anything else. DAD: Now it's you that are pulling at my ear (means pulling my leg)… SON: (laughter) ANNOUNCER: Although you can't always see or smell pesticides, they can affect your skin, eyes, and make you sick. To learn how to protect yourself and your family visit laredhispana.org. Tagline: A message from this station, the United States Environmental Protection Agency and laredhispana.org.	HIJO: Oye Papá, tu que trabajas en el campo, ¿Sabías que hay muchas clases de pesticidas? PAPÁ: ¿A Poco? ¿Dónde aprendiste eso?, ¿en la escuela? HIJO: Si, el maestro nos enseñó que hay protecciones para los trabajadores del campo, como tu *(con un tono de juguetón/sonrisa)* PAPÁ: ¿Y qué aprendiste? HIJO: Que los pesticidas están por todos lados. En las plantas, el suelo, los productos, y también en la ropa. Por eso te tienes que quitar la ropa de trabajo y lavarte bien antes que todo. PAPÁ: Ahora tu eres el que me está jalando el oído a mi HIJO: (risas) LOCUTOR: Aunque no siempre los puedes ver o oler, los pesticidas pueden afectar a tu piel, tus ojos, y hacerte enfermo. Para aprender cómo protegerte a ti y a tu familia, visite laredhispana.org. Tagline: Un mensaje de esta estación, la Agencia de Protección Ambiental de Estados Unidos y laredhispana.org.

LA RED HISPANA

Inicio | Actualidades | Inmigración | Salud

HEAD BANNER TRANSLATION [728X90]
THE INVISIBLE FACTOR
KNOW THE AGRICULTURAL WORKER PROTECTION STANDARD

EL MANEJO SEGURO DE PESTICIDAS

Los pesticidas se aplican de distintas maneras, de forma líquida o aspersiones, en polvos, gránulos o gases. Aunque muchas veces no podemos notar su presencia, se pueden encontrar en las plantas, en el suelo o incluso en residuos en su ropa o herramientas de trabajo. Los pesticidas, por tanto, aunque son un factor invisible, son peligrosos si no sabemos manejarlos responsablemente. Pueden ser muy útiles en el control y manejo de plagas pero también pueden provocar efectos dañinos en las personas que los manipulan o trabajan con ellos.

PESTICIDES SAFE MANAGEMENT

Pesticides are applied in different ways, in a liquid form or as sprays, in powders, granules or gases. Although often we can not notice their presence, they can be found on plants, on the ground or even residues on clothing or work tools. Pesticides, therefore, although they are an invisible factor, can be dangerous if we do not know how to handle them responsibly. They can be very useful in the control and management of pests, but they can also cause risks in the people who manipulate or work with them.

LISTEN TO RADIO PSA

Right SKYSCRAPPER [300x600]

ARE YOU AWARE OF THE INVISIBLE FACTOR?
RECEIVE TRAINING
Pesticides enter our body in many ways
Protect yourself

DAÑOS A LA SALUD

El contacto con los pesticidas o su entrada al cuerpo pueden afectarle después de varios meses o años, aunque usted no perciba síntomas de intoxicación inmediatos.
La exposición a ciertos pesticidas está vinculada a **distintos problemas de salud**:

HEALTH RISKS

Contact with pesticides or their entry into the body can affect you after several months or years, even if you do not perceive immediate symptoms of poisoning. Exposure to certain pesticides is linked to different health problems:

DIGITAL DISPLAY TRANSLATION [940x788]
THE INVISIBLE FACTOR
Know the Standard Protections
Medical Attention: It is a requirement to have address of a nearby medical facility at central location
Do not enter the area: If you see the sign or if they notify you. After applying pesticides wait the recommended time to enter again
Avoid contamination: Make sure pesticides don't contact or drift on other persons nearby
Training: You should receive training about the Standard and how to protect yourself
Access to information: The record with safety information and pesticides use should be kept at a central location.
Cleaning and Decontamination: The employer must provide water, soap and disposables towels for decontamination

Inform yourself about The Agricultural Worker Protection Standard

Skyscraper [160x600]

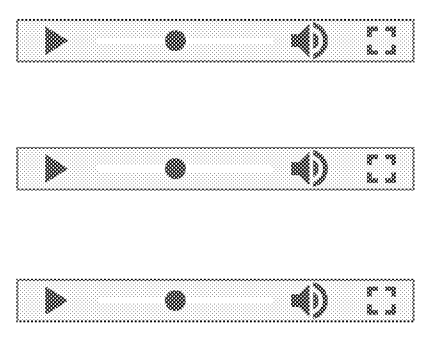
Better Safe than Sorry

Know
The Agricultural Worker Protection Standard

EL MANEJO SEGURO DE PESTICIDAS

Los pesticidas se aplican de distintas maneras, de forma líquida o aspersiones, en polvos, gránulos o gases. Aunque muchas veces no podemos notar su presencia, se pueden encontrar en las plantas, en el suelo o incluso en residuos en su ropa o herramientas de trabajo. Los pesticidas, por tanto, aunque son un factor invisible, son peligrosos si no sabemos manejarlos responsablemente. Pueden ser muy útiles en el control y manejo de plagas pero también pueden provocar intoxicaciones en las personas que los manipulan o trabajan con ellos.

ESCUCHA EL PSA DE RADIO



DAÑOS A LA SALUD

El contacto con los pesticidas o su entrada al cuerpo pueden afectarle después de varios meses o años, aunque usted no perciba síntomas de intoxicación inmediatos.
La exposición a ciertos pesticidas está vinculada a **distintos problemas de salud**:

Message

From: Kaiser, Sven-Erik [Kaiser.Sven-Erik@epa.gov]
Sent: 6/7/2018 1:22:16 AM
To: Keigwin, Richard [Keigwin.Richard@epa.gov]; Beck, Nancy [Beck.Nancy@epa.gov]; Hanley, Mary [Hanley.Mary@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; Palich, Christian [palich.christian@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Baptist, Erik [Baptist.Erik@epa.gov]; Frye, Tony (Robert) [frye.robert@epa.gov]
Subject: Sen Ag TA Request on WPS-Followup
Attachments: designated rep AEZ Udall doc.docx; ATT00001.htm

WPS Team- please see the followup request from Senate Ag regarding revised language on WPS. Their specific question

Deliberative Process / Ex. 5

Sven

Begin forwarded message:

> **From:** "Murray, DaNita (Agriculture)" <DaNita_Murray@ag.senate.gov>
> **Date:** June 6, 2018 at 7:20:55 PM EDT
> **To:** "'Kaiser, Sven-Erik'" <Kaiser.Sven-Erik@epa.gov>, "Vlasaty, Andrew (Agriculture)" <Andrew_Vlasaty@ag.senate.gov>
> **Subject: RE: Sen Ag TA Request on WPS**
>
> It is our intent that this and any related communications will be treated by EPA as Congressional records, and that all of these records remain under the Committee's control.
>
> **Deliberative Process / Ex. 5**
>
> Thank you, regards, DaNita Murray
>
> ---
>
> **From:** Kaiser, Sven-Erik <Kaiser.Sven-Erik@epa.gov>
> **Sent:** Wednesday, June 6, 2018 9:57 AM
> **To:** Vlasaty, Andrew (Agriculture) <Andrew_Vlasaty@ag.senate.gov>; Murray, DaNita (Agriculture) <DaNita_Murray@ag.senate.gov>
> **Subject:** Sen Ag TA Request on WPS
>
> Andrew and DaNita,
> Thank you for the request to provide technical assistance on the draft language.
>
> **Deliberative Process / Ex. 5**

Deliberative Process / Ex. 5

Please let me know if any questions. Thanks,
Sven

Sven-Erik Kaiser
U.S. EPA
Office of Congressional and Intergovernmental Relations
1200 Pennsylvania Ave., NW (1305A)
Washington, DC 20460
202-566-2753 (o)
202-591-0619 (c)

From: Vlasaty, Andrew (Agriculture) [mailto:Andrew_Vlasaty@ag.senate.gov]
Sent: Monday, June 04, 2018 5:20 PM
To: Kaiser, Sven-Erik <Kaiser.Sven-Erik@epa.gov>
Cc: Murray, DaNita (Agriculture) <DaNita_Murray@ag.senate.gov>
Subject: WPS technical assistance

It is our intent that this and any related communications will be treated by EPA as Congressional records, and that all of these records remain under the Committee's control.

Sven, can we have EPA provide technical assistance on the attached? Thanks in advance.

Andrew Vlasaty
Senior Professional Staff
Senate Agriculture Committee
Chairman Pat Roberts (R-KS)
(202) 224-2035

Message

From: Cleland-Hamnett, Wendy [Cleland-Hamnett.Wendy@epa.gov]
Sent: 5/12/2017 9:17:39 PM
To: barb@nasda.org
CC: dudley@nasda.org; Beck, Nancy [Beck.Nancy@epa.gov]; Keigwin, Richard [Keigwin.Richard@epa.gov]; keany.kevin@epa.gov; Jakob, Avivah [Jakob.Avivah@epa.gov]
Subject: Worker Protection Standard Implementation Extension
Attachments: Response to NASDA Petition 5-11-17.pdf

Dr. Glenn,

Please find attached a response to your request that EPA extend the implementation period for the revised Agricultural Worker Protection Standards. We are also sending a signed copy of the letter via the mail.

Please feel free to contact me if you would like to discuss the response, or any other issues on which I can be of help.

Sincerely,

Wendy Cleland-Hamnett
Acting Assistant Administrator
Principal Deputy Assistant Administrator
Office of Chemical Safety & Pollution Prevention
U.S. Environmental Protection Agency
202-564-2910
cleland-hamnett.wendy@epa.gov

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 11 2017

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

Barbara P. Glenn, Ph.D.
Chief Executive Officer
National Association of State Departments of Agriculture
4350 North Fairfax Drive
Suite 910
Arlington, VA 22203

Dear Ms. Glenn:

On February 17, 2017, you requested that the U.S. Environmental Protection Agency (EPA) issue "a public notice to formally extend the implementation of all revised provisions to the Agricultural Worker Protection Standard (WPS)...until at least January 2, 2018, or until adequate enforcement guidance, educational materials, and training resources have been completed and the state lead agencies have the tools, time, and resources necessary to effectively implement the rule changes and assist the regulated community with compliance activities." After careful evaluation, the EPA believes it appropriate to grant your request to extend the implementation of all revised provisions to the Agricultural Worker Protection Standard (WPS) until the necessary guidance and training have been completed which would allow state lead pesticide agencies to successfully implement the rule changes. We will soon begin the regulatory process to formally extend the compliance date for all revised provisions of the WPS. We will keep you informed of our progress.

We appreciate your concern regarding this issue and look forward to working with our state and tribal regulatory partners on this important work.

If you have further questions, please contact me or Kevin Keany in the EPA's Office of Pesticide Programs at keany.kevin@epa.gov or (703)-305-5557.

Sincerely,

Wendy C. Hamnett

Wendy Cleland-Hamnett
Acting Assistant Administrator

Internet Address (URL) • http://www.epa.gov
Recycled/Recyclable • Printed with Vegetable Oil Based Inks on 100% Postconsumer, Process Chlorine Free Recycled Paper

Message

From: Kaiser, Sven-Erik [Kaiser.Sven-Erik@epa.gov]
Sent: 12/14/2017 4:33:35 PM
Subject: EPA Notification on Pesticide Worker Protection and Certified Applicator rules
Attachments: NASDA Update on WPS 12 13 17.pdf

Heads up that today EPA initiated a rulemaking process to revise targeted aspects of the Agricultural Worker Protection Standard (WPS) and the Certification and Training (C&T) Rule. The implementation dates for the existing WPS and C&T rules remain in effect. In addition, EPA updated its response to a petition from NASDA on WPS.

Agricultural Worker Protection Standard (WPS)

Deliberative Process / Ex. 5

Certification and Training (C&T, or Certification of Pesticide Applicators) Rule

Deliberative Process / Ex. 5

National Association of State Departments of Agriculture (NASDA) Petition

Deliberative Process / Ex. 5

Please let me know if any questions. Thanks,
Sven

Sven-Erik Kaiser
U.S. EPA
Office of Congressional and Intergovernmental Relations
1200 Pennsylvania Ave., NW (1305A)
Washington, DC 20460
202-566-2753 (o)
202-591-0619 (c)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

December 13, 2017

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

Barbara P. Glenn, Ph.D.
Chief Executive Officer
National Association of State Departments of Agriculture
4350 North Fairfax Drive, Suite 910
Arlington, VA 22203

Subject: Update on EPA's Implementation of the Agricultural Worker Protection Standard

Dear Dr. Glenn:

The purpose of this letter is to provide you with an update to our May 11, 2017, letter, responding to the request submitted by the National Association of State Departments of Agriculture (NASDA) to extend the implementation of the revisions to the Agricultural Worker Protection Standard (WPS). In the agency's May 2017 response, we indicated our intention to extend the implementation of all revised provisions of the WPS until guidance and training were completed to allow state lead pesticide agencies to successfully implement the new rule.

Since May 2017, agency staff have continued to work collaboratively with the state departments of agriculture to better understand what support states need to implement the new standard. EPA staff have provided additional training, held meetings with agricultural stakeholders, and developed more guidance to help the agricultural community prepare for effective implementation of the revised WPS. Furthermore, the agency has sought feedback from affected stakeholders to identify which aspects of the rule might need clarification and, if necessary, revision. This conversation continued most recently as part of the November 2, 2017, meeting of the Pesticide Program Dialogue Committee (PPDC), a federal advisory committee providing advice to the Office of Pesticide Programs' policy and regulatory decisions. During the November 2017 meeting, the PPDC discussed three issues, also raised as part of the Regulatory Reform effort initiated by the agency in response to Executive Order 13771: 1) minimum age for agricultural handlers, 2) the designated representative provision, and 3) the application exclusion zone.

Based upon consideration of the feedback received over the past several months, the agency has determined that it is not necessary to extend the compliance dates for the revised WPS. EPA will allow the remaining provisions of the revised WPS to go into effect on January 2, 2018. However, in light of the concerns raised in the public comments submitted in response to Executive Order 13771 ("Reducing Regulation and Controlling Regulatory Costs" and Executive Order 13777 ("Enforcing the Regulatory Reform Agenda"), as well as some of the targeted suggestions for change expressed at the PPDC meeting, the EPA intends to issue a proposed rule

Internet Address (URL) • http://www.epa.gov
Recycled/Recyclable • Printed with Vegetable Oil Based Inks on 100% Postconsumer, Process Chlorine Free Recycled Paper

for public comment that would reconsider targeted aspects of the worker protection standard, namely the provisions related to minimum age, the designated representative provision, and the application exclusion zone. The agency will soon issue a notice in the Federal Register that announces that the EPA has initiated a rulemaking process to reconsider these aspects of the revised WPS. That Federal Register notice will also announce that the compliance dates in the revised WPS published on November 2, 2015 remain in effect and that the EPA does not intend to extend them.

The agency looks forward to continuing to work collaboratively with NASDA and all of the state lead pesticide agencies to ensure that agricultural workers are adequately protected when applying pesticides to produce America's food and fiber. In addition, we want to continue our joint efforts to ensure that as we work together to protect public health and the environment, we are also meeting the needs of the rural economy.

Sincerely,

Charlotte Bertrand

Charlotte Bertrand
Acting Principal Deputy Assistant Administrator

Message

From: Keller, Kaitlin [keller.kaitlin@epa.gov]
Sent: 3/28/2018 3:16:22 PM
To: Beck, Nancy [Beck.Nancy@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]
Subject: FW: FIFRA Section 25 Reviews, USDA, SAP & Hill
Attachments: FIFRA Reviews_2010-05-25.pdf

Attached is the FIFRA Review document RCS referred to earlier.

FIFRA section 25(a) (3) and (4) read as follows:

(3) CONGRESSIONAL COMMITTEES.—At such time as the Administrator is required under paragraph (2) of this subsection to provide the Secretary of Agriculture with a copy of proposed regulations and a copy of the final form of regulations, the Administrator shall also furnish a copy of such regulations to the Committee on Agriculture of the House of Representatives and the Committee on Agriculture, Nutrition, and Forestry of the Senate.

(4) CONGRESSIONAL REVIEW OF REGULATIONS.—Simultaneously with the promulgation of any rule or regulation under this Act, the Administrator shall transmit a copy thereof to the Secretary of the Senate and the Clerk of the House of Representatives. The rule or regulation shall not become effective until the passage of 60 calendar days after the rule or regulation is so transmitted.

From: Hofmann, Angela
Sent: Wednesday, January 24, 2018 10:20 AM
To: Bertrand, Charlotte <Bertrand.Charlotte@epa.gov>; Beck, Nancy <Beck.Nancy@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Keigwin, Richard <Keigwin.Richard@epa.gov>; Mosby, Jackie <Mosby.Jackie@epa.gov>; Barone, Stan <Barone.Stan@epa.gov>; Graves, Inza <Graves.Inza@epa.gov>
Cc: Hoyt, Sarita <Hoyt.Sarita@epa.gov>; Smith, Peterj <Smith.Peterj@epa.gov>; Chun, Melissa <Chun.Melissa@epa.gov>; Keller, Kaitlin <keller.kaitlin@epa.gov>; Hanley, Mary <Hanley.Mary@epa.gov>
Subject: FIFRA Section 25 Reviews, USDA, SAP & Hill

As follow-up to our conversation this morning about FIFRA external reviews. Although the reviews cannot be waived, the timeframes associated with them can be waived or modified with agreement. We previously worked with OGC to prepare the attached summary of this requirement -- you all might find it helpful as we consider this mandate for the WPS rules.

Message

From: Berwald, Derek [Berwald.Derek@epa.gov]
Sent: 3/15/2018 10:50:27 PM
To: Beck, Nancy [Beck.Nancy@epa.gov]; Bertrand, Charlotte [Bertrand.Charlotte@epa.gov]; Keller, Kaitlin [keller.kaitlin@epa.gov]; Hughes, Hayley [hughes.hayley@epa.gov]; Keigwin, Richard [Keigwin.Richard@epa.gov]; Miller, Wynne [Miller.Wynne@epa.gov]; Kiely, Timothy [Kiely.Timothy@epa.gov]; Wyatt, TJ [Wyatt.Tj@epa.gov]; Lee, Andrew [Lee.Andrew@epa.gov]; Mosby, Jackie [Mosby.Jackie@epa.gov]; Keaney, Kevin [Keaney.Kevin@epa.gov]; Davis, Kathy [Davis.Kathy@epa.gov]; Kasai, Jeanne [Kasai.Jeanne@epa.gov]; Rivera-Lupianez, Ana [Rivera-Lupianez.Ana@epa.gov]; Park, Jennifer [park.jennifer@epa.gov]; Pont, Richard [Pont.Richard@epa.gov]; Perlis, Robert [Perlis.Robert@epa.gov]; Garrison, Scott [Garrison.Scott@epa.gov]
CC: Parrott, Patricia [parrott.patricia@epa.gov]
Subject: RE: WPS EA Discussion
Attachments: Steinberg 2005 Cognitive Adolesence.pdf; Golub 2000.pdf; Dayan et al_2010_Adolescent brain and risk taking.pdf; Calvert 2003.pdf; Reed 2006 PPE Behavior.pdf; Salazar 2004 Hispanic Adolescents.pdf; Steinberg and Cauffman 1996 Maturity of Judgement in Adolescents.pdf; abdel Rasoul pesticide egypt..pdf; Sanborn 2007 Non-Cancer Health Effects Family Physician.pdf; young and rischitelli 2008 risks hispanic adolescent farmworkers.pdf; Casey 2008 Adolescent Brain.pdf; Rice and Barone 2000 smaller file size.pdf

Charlotte asked for copies of the references. PDFs are attached.

The EPA Child Specific Exposure Handbook is very large, so I'll include a link:
file:///C:/Users/dberwald/Downloads/CSEFH_08FINAL.PDF

This Institute for Highway Safety (2008) is better viewed on the web:
http://www.iihs.org/iihs/topics/t/teenagers/fatalityfacts/teenagers/2008

I am missing one reference: Rowntree DA, L Stallones, PL Sample, and K Sweitzer. 1998. Perceptions of Farm Hazards and Personal Safety Behavior among Adolescent Farmworkers, Journal of Agricultural Safety and Health. Special Issue (1):159-169.

db

-----Original Appointment-----
From: Beck, Nancy
Sent: Thursday, March 15, 2018 10:59 AM
To: Beck, Nancy; Bertrand, Charlotte; Keller, Kaitlin; Hughes, Hayley; Keigwin, Richard; Miller, Wynne; Kiely, Timothy; Berwald, Derek; Wyatt, TJ; Lee, Andrew; Mosby, Jackie; Keaney, Kevin; Davis, Kathy; Kasai, Jeanne; Rivera-Lupianez, Ana; Park, Jennifer; Pont, Richard; Perlis, Robert; Garrison, Scott
Cc: Parrott, Patricia
Subject: WPS EA Discussion
When: Thursday, March 15, 2018 4:00 PM-4:45 PM (UTC-05:00) Eastern Time (US & Canada).
Where: **Conference Line/Code / Ex. 6**

NeuroToxicology 29 (2008) 833–838

Contents lists available at ScienceDirect

NeuroToxicology

Effects of occupational pesticide exposure on children applying pesticides

Gaafar M. Abdel Rasoul [a], Mahmoud E. Abou Salem [a], Atef A. Mechael [a], Olfat M. Hendy [b], Diane S. Rohlman [c,*], Ahmed A. Ismail [a]

[a] Community, Environmental and Occupational Medicine Department, Faculty of Medicine, Menoufia University, Shebin Elkom, Egypt
[b] Clinical Pathology Department, National Liver Institute, Menoufia University, Shebin Elkom, Egypt
[c] Center for Research on Occupational and Environmental Toxicology, Oregon Health and Sciences University (OHSU), Portland, OR 97239, USA

ARTICLE INFO

Article history:
Received 10 February 2008
Accepted 25 June 2008
Available online 9 July 2008

Keywords:
Neurobehavioral tests
Adolescents
Pesticides
AChE
Seasonal applicators

ABSTRACT

Nearly 40% of the Egyptian workforce is employed in agriculture. The cotton industry relies on children and adolescents, who work seasonally, to apply pesticides to the cotton crops. Although previous research has examined adult pesticide exposures in this workforce in Egypt, no research has examined the health effects in adolescents. This study attempts to systematically replicate findings examining the impact of organophosphate pesticide (OP) exposure in adults on Arabic speaking children working as applicators. The aim of this study was to examine the impact of pesticide exposure on children and adolescents spraying cotton fields. Male children currently applying pesticides between the ages of 9 and 15 (Younger, $n = 30$) and 16 and 19 (Older, $n = 20$) were recruited for the study. They completed a neurobehavioral test battery; personality inventory; work, health, and exposure questionnaires; and medical and neurological screening exams. Blood samples were collected to measure acetylcholinesterase. Children not working in agriculture, matched on age and education, served as controls. Both Younger and Older applicator groups, performed significantly worse than the controls on the majority of neurobehavioral tests controlling for age and years of education. The applicators reported significantly more neurological symptoms than the controls and had lower acetylcholinesterase activity. A dose–effect relationship demonstrated that increased years of exposure to organophosphate pesticides is associated with cognitive deficits. This is one of the several studies demonstrating that functional cognitive effects are positively correlated with increased years of exposure to OP pesticides, though primarily in adult populations, building confidence in the association. Since children around the world are exposed to OP pesticides, these studies suggest that the need to evaluate this potential problem is urgent.

© 2008 Elsevier Inc. All rights reserved.

1. Introduction

Agriculture is the largest employer in Egypt, employing nearly 40% of the Egyptian workforce (Andersen, 2003). The cotton crop is the primary agricultural product and is highly regulated by the Egyptian Ministry of Agriculture (Rizk, 1999). Pesticides, including organophosphorus pesticides (OPs), are used in Egypt on the cotton crop with large quantities being applied relative to other crops (Mansour, 2004). Children and adolescents work seasonally in the cotton fields applying pesticides.

Adult pesticide applicators and workers who were poisoned by or had high exposures to OP pesticides have reported a broad range of non-specific and neurological symptoms, demonstrated neuropsychological deficits and personality changes, and had acetylcholinesterase (AChE) inhibition associated with exposure to those pesticides. Non-specific symptoms following high exposures have included headache, dizziness, fatigue, weakness, nausea, chest tightness, and difficulty in breathing (Kamel and Hoppin, 2004).

Workers exposed to OP pesticides also demonstrate neurobehavioral deficits on response speed and coordination, sustained attention, visual perception and memory, and complex functioning (Kamel et al., 2003). These studies found that an increasing degree of neurobehavioral deficits were associated with more years working in agriculture and handling pesticides (Rohlman et al., 2007; Roldan-Tapia et al., 2005). An increase in neurological symptoms and neurobehavioral deficits in verbal abstraction, visuomotor speed, problem solving, attention, and memory was

* Corresponding author at: CROET, L606, Oregon Health and Sciences University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA. Tel.: +1 503 494 2513; fax: +1 503 494 4278.
E-mail address: rohlmand@ohsu.edu (D.S. Rohlman).

Abbreviations: AChE, acetylcholinesterase; NB, neurobehavioral; PPE, personal protective equipment; WAIS, Wechsler Adult Intelligence Scale; BVRT, Benton Visual Retention Test; BMI, body mass index.

0161-813X/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuro.2008.06.009

shown in adult pesticide workers in Egypt compared to controls (Farahat et al., 2003).

There has been concern about the impact of pesticides on children and adolescents. Children are considered to be more vulnerable due to the significant anatomical and maturational changes occurring in the brain during developmental periods including adolescence (Andersen, 2003), and also the increasing findings of animal studies indicating neurodevelopment effects of pesticides (Johnson et al., 1998; Moser and Padilla, 1998). Although several studies have examined children who live in agricultural communities or whose parents work in agriculture (Handal et al., 2007; Rohlman et al., 2005), only a few studies have examined adolescents who are currently working in agriculture. Adolescent farm workers in Brazil had motor and attention deficits associated with an exposure index derived by interview (Eckerman et al., 2007). US adolescents working in agriculture had significantly worse performance than adolescents not working in agriculture in attention, memory and visuomotor domains (Rohlman et al., 2001) and increased years working in agriculture and applying pesticides was also associated with neurobehavioral performance deficits in adolescent workers (Rohlman et al., 2007).

This study examined neurobehavioral performance in children seasonally exposed to OP pesticides to test the hypothesis (suggested by Kamel et al., 2003; Rohlman et al., 2007; Roldan-Tapia et al., 2005) that increasing exposure to OP pesticides is associated with progressively larger neurobehavioral deficits, in a population likely to have higher exposure than those previously studied.

2. Methods

2.1. Participants

This study was conducted from June to August 2005, during the pesticide application period to the cotton crop. It was carried out at Shebin Elkom District, Menoufia governorate, Egypt. During this time, the local agricultural office hired approximately 10 children from each village to apply pesticides to the cotton crop under the supervision of adult engineers and agricultural employees. Five villages out of 50 from the Shebin Elkom District were randomly chosen to recruit children working as pesticide applicators as study participants. Male children between the ages of 9 and 18 years currently working as applicators were invited to participate in the cross-sectional study. These children were seasonal workers that spray pesticides in the cotton fields with backpack applicators. There were a total of 56 children working in these 5 villages. Six children declined to participate, yielding a response rate of 89.3%. A control group of children who had never worked in the cotton fields were selected from the friends and relatives of the applicator children. These children lived in the same community as the children who were applicators and attended the same schools. The applicator and control children were divided by age into two groups, Younger (9–15 years of age) and Older (16–18 years of age).

2.2. Pesticide application

The pesticide applications for the cotton crop are highly regulated in Egypt and the Ministry of Agriculture has specific guidelines that are followed throughout the country. Each cotton field in Egypt is subject to four application cycles per season and each application lasts 5–11 days: Cycle (1) *Bacillus thuringiensis* (a natural occurring bacterium that is harmful to insects but not humans); Cycle (2) Pestban (chlorpyrifos) OP application; Cycle (3) Pyrethrins or a less potent carboxylate; and Cycle (4) Dursban (another formulation of chlorpyrifos). There is approximately a week of no spraying between the four application periods and the total working days for the children were approximately 30 days. This schedule of pest management has been followed rigidly for over 10 years. The typical workday was from 8:00 a.m. to 12:00 p.m. and then from 3:00 p.m. to 7:00 p.m., 6 days per week. Organophosphate pesticides were applied during the second and fourth cycles, from the end of June through the first week of July and during the second week of August.

Agremond backpack sprayers that hold 20 L are worn by the applicators to apply the pesticides. Spraying was carried out by a team of seasonal workers consisting of 7–12 applicators. Applicators are trained by the supervisors to use the backpack sprayers on their first day of work. For the applicators, the typical workday begins at the local agricultural office to receive the backpack sprayers and pesticides. The amount of pesticides applied varies each day depending on the size of the fields to be sprayed and the degree of pest infestation in the fields. Once in the fields, an engineer from the local agricultural office prepares the mixture and loads the backpack sprayers. He also supervises the application process throughout the day. The sprayers are reloaded multiple times during the day until the spraying is completed. Beside the engineers, there are also assistants, and mechanics in the field to oversee the application and maintain the equipment.

Although some personal protective equipment (PPE) is available at the local agricultural office and the applicators have access to it, there are no regulations in Egypt requiring PPE, there is no formal training on its use and it is not commonly used by the applicators. Some wear dust masks and safety glasses to prevent splashes, but this was not the norm in 2005. The main routes of exposure are dermal exposure and inhalation.

2.3. Procedures

Written consent was obtained from the children and their legal guardian. The study was reviewed and accepted by the Medical Ethics committee of the Faculty of Medicine, Menoufia University on July 13, 2005. The children were examined at the end of the workday in a clinic near to their resident villages during the last week of the spraying season.

The children, with the assistance of their parents, completed a questionnaire describing their medical and work history, including information about their exposure to pesticides. A detailed clinical medical examination and a complete neurological examination were administered by specialists. Five milliliters of blood was drawn from all participants and serum AChE was determined according to Weber (1966) using standard kits (Test-combination Boehringer Mannheim GmbH Diagnostica). Serum or plasma AChE was selected because it is a better short-term indicator of cholinesterase inhibition than red blood corpuscles (RBCs) AChE due to its more rapid response to exposure; it is used as an indicator of recent, acute exposure to cholinesterase inhibiting pesticides. Also, because the primary pesticide being applied is chlorpyrifos, which has a preferentially inhibiting effect on serum AChE rather than RBC AChE (Furman, 2006).

Age appropriate versions of the Wechsler Adult Intelligence Scale (WAIS) that were validated in an Arabic speaking population were used to assess neurobehavioral function (Table 1; Abdel-Khalek, 1994). A subset of the tests, Information, Similarities, Arithmetic, and Block Design, had different versions for children ($\leq$15 years) and adults (>15 years) participants. The remaining tests in the battery, Digit Span, Benton Visual Retention Test (BVRT), and Trail Making, do not have separate versions for adults and children. Better performance is evaluated by higher scores obtained on tests of Information, Similarities, Arithmetic, Digit Symbol, Block Design, Digit Span, and the Benton Visual Retention Test. In contrast, lower latencies or time to complete Trail Making A and B indicate better

Table 1
Name of neurobehavioral test, function, and brief description of the items

Tests	Function	Description
Information	Information and intelligence	30 general information questions for children and 25 for adults
Similarities	Ability to concentrate, abstract thinking and intelligence	16 pairs of words for children and 12 pairs for adults
Arithmetic	Attention and concentration	16 combined oral and written items for children and 10 for adults
Block Design	Spatial relations	Children construct designs using 9 blocks and 10 cards and adults use 16 blocks and 9 cards
Digit Span (Forward, Reverse, Total)	Short-term auditory memory	Sets of three to nine digits, the longest string of digits repeated is the score
Digit Symbol	Perceptual memory speed	90 s to fill in blank squares with correct symbol that matches a digit
BVRT	Short-term visual memory	Participant had 10 s to look at a card, then after 15 s interval is asked to reproduce the drawing
Trail Making (A and B)	Attention, visual conception	Draw a line connecting numbers to numbers (Trail A) and letters to numbers in the correct order (Trail B)

performance. Examiners were blind to the status of the participant as applicator or control. The Eysenck Personality Questionnaire (EPQ) was used to measure personality. It is formed of 90 questions that assess four aspects of personality; psychoticism, neuroticism, extraversion, and criminality (in addition to the lie scale). A child version was used for participants ≤15 years old.

2.4. Statistical analysis

SPSS Version 14.0 was used to analyze the data. The *t*-test was used to examine the differences between means, the χ^2-test was used to examine the differences between percentages, and Pearson's correlation was used to examine the correlation between quantitative variables. Holm's correction of *p*-values was used to adjust the level of significance (Holm, 1979). Multiple linear regression was used to estimate difference in average performance for control and applicator participants while adjusting for effects of age and education. The difference in performance between these two groups was adjusted to reflect a 13-year-old individual with 6 years of education and a body mass index (BMI) of 21.7 for Younger participants or a 17-year-old individual with 9 years of education and a BMI of 25.1 for Older participants. A second multiple linear regression model was constructed to estimate the partial correlation of NB performance with days worked this season, years worked and AChE, controlling for age, and its interaction with all of these variables.

3. Results

3.1. Demographic characteristics

There were no significant differences on age, years of education or smoking between the applicator and control groups in both the Younger and Older children. However, for the Older children the body mass index of the control children ($\bar{x} = 26.9$; S.D. = 4.1) was significantly higher than that of the applicator children ($\bar{x} = 23.2 \pm 0.6$) ($t = 3.6$; $p < 0.05$).

3.2. Duration of work and AChE

The applicator children reported working as pesticide applicators an average of 5 years (range of 1–9 years). During the current application season they reported working between 3 and 30 days with an average of 20 days. There was no significant difference in days worked during the current season between the Younger applicators ($\bar{x} = 19.6$; S.D. = 8.6) and Older applicators ($\bar{x} = 21.4$; S.D. = 6.7) ($t = 0.8$; $p > 0.05$). However, the Older participants reported working significantly more years ($\bar{x} = 7.2$; S.D. = 1.5) than the Younger participants ($\bar{x} = 3.5$; S.D. = 1.6) ($t = 3.7$; $p < 0.001$). Acetylcholinesterase was measured in both the applicator and control groups. A significant lower activity level of AChE was found in the applicator group ($\bar{x} = 239.8$; S.D. = 60.0 IU/L) compared to the control group ($\bar{x} = 283.1$; S.D. = 61.6 IU/L) ($t = 3.6$; $p < 0.05$).

3.3. Neurobehavioral performance

The applicator groups had significantly impaired neurobehavioral performance (NB) on all of the measures compared to the control groups (Tables 2 and 3). The effect sizes ranged from small (0.2) to large (0.8), using Cohen's classification (1988). After accounting for age and education there was no significant impact of BMI on predicting neurobehavioral performance. The impact of age on modifying NB performance was examined on the tests that were the same for both groups (Digit Span, Digit Symbol, BVRT, Block Design, Trail Making A and B). Age had a significant impact on the BVRT and Digit Span test. For the BVRT, there was a significant

Table 2
Neurobehavioral performance in the Younger (9–15 years) applicator ($n = 30$) and control ($n = 30$) groups

	Adjusted mean[a] (S.E.)		*B* coefficient	95% C.I.	*p*-Value[b]	Effect size
	Applicator	Control				
Information	20.9 (0.4)	23.4 (0.4)	−2.5	−3.7 to −1.3	<0.001	0.5
Arithmetic	6.2 (0.6)	8.7 (0.6)	−2.5	−4.2 to −0.9	0.02	0.4
Similarities	18.1 (0.3)	20.8 (0.3)	−2.7	−3.6 to −1.7	<0.001	1.0
BVRT	4.4 (0.3)	5.9 (0.3)	−1.5	−2.3 to −0.6	0.01	0.6
Digit Span Forward	5.4 (0.2)	6.1 (0.2)	−0.7	−1.3 to −0.2	0.02	0.3
Digit Span Backward	4.7 (0.2)	5.5 (0.2)	−0.9	−1.5 to −0.3	0.03	0.3
Digit Span Total	10.1 (0.4)	11.7 (0.4)	−1.6	−2.7 to −0.5	0.02	0.3
Block Design	33.2 (1.0)	40.0 (1.0)	−6.8	−9.6 to −3.9	<0.001	0.6
Trail Making A	55.4 (1.0)	48.8 (1.0)	6.6	4.8 to 10.4	<0.001	1.3
Trail Making B	108.7 (1.4)	104.3 (1.5)	4.5	0.3 to 8.6	0.04	1.3

[a] Adjusted to reflect mean performance for a 13-year-old person with 6 years of education and 21.7 BMI.
[b] Holm's corrected *p*-value, adjusted for 10 tests.

Table 3
Neurobehavioral performance in the Older (16–18 years) applicator ($n = 20$) and control ($n = 20$) groups

	Adjusted mean[a] (S.E.)		*B* coefficient	95% C.I.	*p*-Value[b]	Effect size
	Applicator	Control				
Information	16.6 (0.4)	18.4 (0.4)	−1.8	−3.0 to −0.6	0.005	0.1
Arithmetic	5.5 (0.4)	9.1 (0.4)	−3.6	−4.7 to −2.5	<0.001	0.2
Similarities	15.9 (0.2)	18.9 (0.2)	−3.0	−3.6 to −2.4	<0.001	0.4
BVRT	4.6 (0.2)	6.3 (0.2)	−1.7	−2.2 to −1.2	<0.001	0.2
Digit Span Forward	4.0 (0.1)	5.9 (0.1)	−1.9	−2.3 to −1.6	<0.001	1.0
Digit Span Backward	3.5 (0.2)	5.5 (0.2)	−2.0	−2.5 to −1.5	<0.001	1.0
Digit Span Total	7.5 (0.3)	11.3 (0.3)	−3.7	−4.5 to −3.0	<0.001	0.5
Block Design	18.3 (0.7)	26.1 (0.7)	−7.7	−9.6 to −5.8	<0.001	0.1
Digit Symbol	25.2 (0.8)	33.5 (0.7)	−8.4	−10.5 to −6.2	<0.001	0.4
Trail Making A	60.4 (0.8)	54.1 (9.8)	6.3	4.1–8.6	<0.001	0.3
Trail Making B	118.8 (1.2)	111.9 (1.1)	6.8	3.5–10.1	<0.001	0.1

[a] Adjusted to reflect mean performance for a 17-year-old person with 9 years of education and 25.1 BMI.
[b] Holm's corrected *p*-value, adjusted for 11 tests.

interaction between exposure and age ($p < 0.001$), for a participant with 6.6 years of education, BVRT scores of the controls increased 0.3 units for each additional year of age, while decreasing 0.3 units for each year of age among applicators. There was also a significant interaction on the Digit Span test between exposure and age ($p = 0.001$). For a participant with 6.6 years of education, Digit Span scores of controls increased 0.2, 0.3, and 0.8 units for each additional year of age for Digit Span Forward, Backward, and Total scores, respectively, while decreasing 0.5, 0.4, and 0.6 units for each year of age among applicators for Digit Span Forward, Backward, and Total, respectively.

Both the Younger and Older applicators scored significantly higher on the neuroticism (mean of 10.0 for both Younger and Older, respectively) and extraversion scales (mean of 13.2 for both Younger and Older, respectively) than the control participants (mean of 9.2 for both Younger and Older on the neuroticism scale and mean of 11.9 for both Younger and Older on the extraversion scales).

3.4. Neurological symptoms

The neurological examination revealed an increase in neurological symptoms in the applicator group compared to the control group. The χ^2-test demonstrated that significantly more participants in the applicator group had blurred vision (28%), dizziness (24%), difficulty in concentration (24%), trouble in remembering (24%), feelings of depression (26%), irritability (22.%), numbness (18%), and fatigue (30.0%), compared to the control participants (8%, 8%, 8%, 6%, 10%, 6%, 2%, and 10%, respectively) ($p < 0.05$). The same results were obtained when the Younger and Older groups were analyzed separately.

Applicator children who report at least three of the following neurological symptoms, blurred vision, dizziness, headache, difficulty in concentration, trouble in remembering, difficulty in understanding, feeling depressed and irritable, numbness, low back pain, and fatigue, worked significantly more days ($\bar{x} = 27.4$; S.D. = 4.1) during the current season than applicator children who report less than three symptoms ($\bar{x} = 16.7$; S.D. = 6.8) ($t = 6.0$; $p < 0.001$). Applicator children who report at least three of the previously mentioned neurological symptoms also worked significantly more years applying pesticides ($\bar{x} = 6.2$; S.D. = 2.4) than applicator children who report less than three symptoms ($\bar{x} = 4.3$; S.D. = 2.1) ($t = 3.0$; $p < 0.05$).

Table 4
Correlation (partial) of the neurobehavioral performance with duration of work (days worked in current season and years worked as an applicator) and AChE

Neurobehavioral tests	*r*		
	Days worked	Years worked	AChE
Information	−0.6**	−0.1	0.4*
Arithmetic	−0.7**	−0.1	0.3
Similarities	−0.5**	−0.4*	0.2
BVRT	−0.8**	0.2	0.1
Digit Span Forward	−0.3	−0.2	0.4*
Digit Span Backward	−0.1	−0.2	0.4*
Digit Span Total	−0.2	0.0	0.4*
Block Design	−0.3*	−0.6**	0.2
Digit Symbol	−0.4	0.1	−0.2
Trail Making A	0.1	0.2	−0.1
Trail Making B	0.4*	0.5**	−0.3*

*$p < 0.05$, **$p < 0.001$.

3.5. Correlation of neurobehavioral performance with AChE, duration of work

Partial correlation of NB performance with the days worked this season, years worked as pesticide applicators and AChE was estimated by constructing a regression model controlling for age, and its interaction with days or years worked (Table 4). A significant correlation between the days worked during the current season was found with performance on 6 of the 11 measures. The Information, Arithmetic, Similarities, BVRT, and Block Design subtests had significant negative correlations and Trail Making B had a significant positive correlation ($p < 0.05$). Years worked as pesticide applicators showed a significant correlation with 3 of the 11 measures, BVRT, Block Design, and Trail Making ($p < 0.05$). A significant correlation between AChE and 5 of the 11 measures was also found (Information, Digit Span Forward, Backward, and Total, and Trail Making B; $p < 0.05$).

4. Discussion

This study reveals significant health effects in children who work as pesticide applicators compared to control children. Children who apply pesticides show impaired neurobehavioral performance, report more symptoms, and have lower AChE activity levels than children from the same communities that do not apply pesticides. This study also shows a correlation between days worked during the current season and total years worked as an applicator and the reporting of symptoms and neurobehavioral performance which provides evidence of a dose–response relationship between exposure and both symptoms and neurobehavioral performance. The strong relationship between the exposure to pesticides and decrement in the different functions of NB

performance is also confirmed by the presence of significant correlations between the days worked this season on 6 of the 11 NB tests (Information, Arithmetic, Similarities, BVRT, Block Design, and Trail Making), while the years worked as an applicator had significant correlations with 3 of the 11 NB tests (BVRT, Block Design, and Trail Making B) after controlling for age, and its interaction with the days and years worked. This confirms other research results (e.g. Roldan-Tapia et al., 2005), that also found a significant relationship between the period of exposure and working in applying OP pesticides and performance deficits and increased neurological symptoms.

This is the first study in children to demonstrate a dose–response relationship between functional cognitive effects, where these functions are positively correlated with increased years of exposure to OP pesticides. These findings confirm previous reports of a relationship between increased years working in agriculture and increased performance deficits found in adult and adolescent workers (Kamel et al., 2003; Rohlman et al., 2007; Roldan-Tapia et al., 2005). The demands of the job require the adolescents to work long days in hot and humid conditions. Although these could contribute to an increased reporting of symptoms of fatigue and irritability, other studies with adult populations report similar findings (Farahat et al., 2003; Stallones and Beseler, 2002). Furthermore, both the applicator and control participants are used to working long hours in these conditions, which make it unlikely that working conditions and not pesticide exposure are the cause of the increased symptoms reporting in the applicator children.

This decrement of neurobehavioral performance, and reporting of more neurological symptoms in the applicator participants, is consistent with a previous study that examined adult pesticide workers in Egypt (Farahat et al., 2003) which found significant deficits in complex visual-motor processing and executive function, verbal abstraction, attention and short-term memory and memory/problem solving/perception. The exposure of the adults was similar to the current study and some of the measures were the same across studies (Fig. 1). Other studies in Egyptian populations comparing adult pesticide applicators to controls have also reported increased neurological, neuromuscular, and psychological symptoms (Amr, 1999), and psychiatric disorders (Amr et al., 1997).

The applicator children show decreased BMI. Organophosphates (OP) exposure has been reported to reduce food intake (Campbell and Hayes, 1974) and may cause these differences. However, an examination of the BMI of both the applicator and control groups shows that it is within the normal range of 18.5–22.5 (WHO, 1995). BMI was included as a covariate in the analysis and was not found to impact performance on the neurobehavioral tests.

Our results also show that there was a significantly lower activity level of AChE in the applicator children compared to the control children. AChE is used as a biomarker for exposure to OP pesticides (von Osten et al., 2004) and the states of Washington and California require cholinesterase monitoring for pesticide applicators. However, because of individual variability, these require a baseline measure and a second measure to indicate a significant depression in cholinesterase activity (Stefanidou et al., 2003). In spite of this recommendation, there are several studies that report only a single cholinesterase level and show a consistent significant association between exposure to pesticides and cholinesterase inhibition in farm workers. Nine studies investigated the effect of pesticide exposure on AChE in pesticide applicators. Three of them measured the AChE before and after exposure and found a significant inhibition in its activity after exposure (Abu Mourad, 2005; Ames et al., 1989; Ohayo-Mitoko et al., 1999). The other studies measured AChE at a single time point and compared it with AChE from a control group. All studies found AChE was significantly lower in the exposed participants than the controls (Chadee and Le Maitre, 1991; Farahat et al., 2003; Misra et al., 1988; Patil et al., 2003; Safi et al., 2005; Srivastava et al., 2000). These findings were replicated in the present study. There was also no significant difference in AChE between the

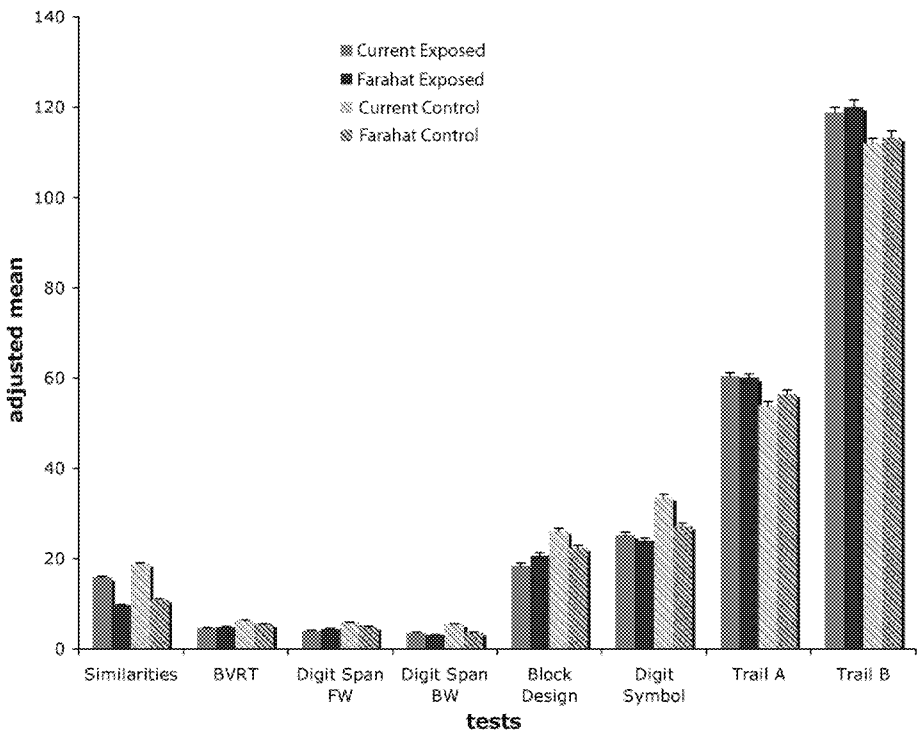


Fig. 1. Neurobehavioral performance of the Older participants in the current study and adult participants from Farahat et al. (2003).

Younger and Older participants either in the applicator or control groups.

The applicator participants also reported more neurological symptoms and scored higher on the personality traits of psychoticism and neuroticism. These findings are similar to other studies with adult workers (Farahat et al., 2003; Kamel and Hoppin, 2004). Two studies in Egyptian populations comparing adult pesticide applicators compared to the controls have reported increased neurological, neuromuscular, and psychological symptoms (Amr, 1999), and psychiatric disorders (Amr et al., 1997).

Applicator children who reported neurological symptoms worked significantly more days than applicator children who do not report these symptoms. They also worked more years than children who do not report these symptoms. These results are similar to studies with adults which found that increased time spent working is associated with increased symptom reporting (Farahat et al., 2003; Kamel et al., 2003; Rohlman et al., 2007).

The association between the level of AChE and neurobehavioral performance, was confirmed by presence of significant correlations between the AChE activity level and the Information, Digit Span and Trail Making tests. These findings address the concerns raised by Roldan-Tapia et al. (2005), about the relationship between NB performance and inhibition of AChE.

There are some limitations of the current study. First, exposure was not limited a specific pesticide. Other pesticides and growth enhancers are applied during the application period including Pyrethroids and Agerin (a biological pesticide). Also, measurement of AChE at only one time point after the spraying season does not provide a measure of the AChE variability of individuals (Stefanidou, 2005). However, these results provide information about a dose–response relationship with duration of exposure and increased impairment in children working as pesticide applicators. They provide a first step as part of larger plan to develop interventions and training to reduce pesticide exposure in applicators.

5. Conclusion

This study showed that children and adolescents who apply pesticides in the cotton fields have significantly lower neurobehavioral performance, report more symptoms and have lower activity levels of serum AChE compared to a control group. The neurobehavioral deficits demonstrated a dose–response relationship between days and years of exposure and NB performance and symptom reporting. Since children around the world are exposed to OP pesticides, these studies suggest the need to evaluate this potential problem is urgent.

Acknowledgments

The study was performed in the Public Health and Community Medicine Department, Faculty of Medicine, Menoufia University, Shebin Elkom, Egypt. We thank the children, adolescents and their parents for their participation in the study. We thank also Dr. Khaled Zyada, the Psychology lecturer, Faculty of Arts, Menoufia University, Egypt, for his help in the selection and administration of the appropriate neurobehavioral tests. We thank also Michael Lasarev, for his help in the statistical analysis.

This manuscript is a part of the MD thesis of Ahmed A. Ismail for his fulfillment of the Doctor Degree in Industrial Medicine and Occupational Health. The entire work was conducted and funded by the Faculty of Medicine, Menoufia University, Egypt. The study was reviewed and accepted by the Medical Ethics committee of the Faculty of Medicine, Menoufia University on July 13 2005.

References

Abdel-Khalek AM. Development of personality traits. J Contemp Psychol (Egypt) 1994;3:29–54 [in Arabic].

Abu Mourad T. Adverse impact of insecticides on the health of Palestinian farm workers in Gaza strip: a hematological biomarker study. Int J Occup Environ health 2005;11:144–9.

Ames RG, Brown SK, Mengle DC, Kahn E, Stratton JW, Jackson RJ. Cholinesterase activity depression among Californian agricultural pesticide applicators. Am J Ind Med 1989;15:143–50.

Amr MM. Pesticide monitoring and its health problems in Egypt, a third world country. Toxicol Lett 1999;107:1–13.

Amr MM, Halim ZS, Moussa SS. Psychiatric disorders among Egyptian pesticide applicators and formulators. Environ Res 1997;73:193–9.

Andersen SL. Trajectories of brain development: point of vulnerability or window of opportunity. Neurosci Biobehav Rev 2003;27:3–18.

Campbell TC, Hayes JR. Role of nutrition in the drug metabolizing system. Pharmacol Res 1974;26:171–97.

Chadee DD, Le Maitre A. Serum cholinesterase levels of vector control workers in Trinidad West Indies (1979–1987). Ann Trop Med Parasitol 1991;85(3):345–8.

Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. New York: Academic press; 1988.

Eckerman DA, Gimenes LS, de Souza RC, Lopes Galvão PR, Sarcinelli PN, Chrisman JR. Age related effects of pesticide exposure on neurobehavioral performance of adolescent farm workers in Brazil. Neurotoxicol Teratol 2007;29:164–75.

Farahat TM, Abdelrasoul GM, Amr MM, Shebl MM, Farahat FM, Anger WK. Neurobehavioral effects among workers occupationally exposed to organophosphorous pesticides. Occup Environ Med 2003;60(4):279–86.

Furman J. Cholinesterase monitoring for agricultural pesticide handlers guidelines for health care providers in Washington State. Department of Labor & Industries. WISHA Policy & Technical Services; 2006.

Handal A, Lozoff B, Breilh J, Harlow S. Neurobehavioral development in children with potential exposure to pesticides. Epidemiology 2007;18(3):312–20.

Holm S. A simple sequentially rejective Bonferroni test procedure. Scand J Stat 1979;6:65–70.

Johnson DE, Seidler FJ, Slotkin TA. Early biochemical detection of delayed neurotoxicity resulting from developmental exposure to chloropyrifos. Brain Res Bull 1998;45(2):143–7.

Kamel F, Hoppin JA. Association of pesticide exposure with neurologic dysfunction and disease. Environ Health Perspect 2004;112:950–8.

Kamel F, Rowland A, Park L, Anger W, Baird D, Gladen B, et al. Neurobehavioral performance and work experience in Florida farmworkers. Environ Health Perspect 2003;111:1765–72.

Mansour SA. Pesticide exposure—Egyptian scene. Toxicology 2004;198:91–115.

Misra UK, Nag D, Khan WA, Ray PK. A study of nerve conduction velocity, late responses and neuromuscular synapse functions in organophosphate workers in India. Arch Toxicol 1988;61:496–500.

Moser VC, Padilla S. Age- and gender-related differences in the time course of behavioral and biochemical effects produced by oral chlorpyrifos in rats. Toxicol Appl Pharmacol 1998;149(1):107–19.

Ohayo-Mitoko GJ, Kromhout H, Karumba PN, Boleij JS. Identification of determinants of pesticide exposure among Kenyan agricultural workers using empirical modelling. Ann Occup Hyg 1999;43:519–25.

Patil JA, Patil AJ, Govindwar SP. Biochemical effects of various pesticides on sprayers of grape gardens. Ind J Clin Biochem 2003;18(2):16–22.

Rizk LY. The white gold calamity. Al-Ahram Weekly 29 July–4 August 1999;440.

Rohlman DS, Arcury TA, Quandt SA, Lasarev M, Rothlein J, Travers R, et al. Neurobehavioral performance in preschool children from agricultural and non-agricultural communities in Oregon and North Carolina. Neurotoxicology 2005;26:589–98.

Rohlman DS, Bailey SR, Anger WA, McCauley L. Assessment of neurobehavioral function with computerized tests in a population of Hispanic adolescents working in agriculture. Environ Res 2001;85:14–24.

Rohlman DS, Lasarev M, Anger WK, Sherer J, Stupfel J, McCauley L. Neurobehavioral performance of adults and adolescent agricultural workers. Neurotoxicology 2007;28(2):374–80.

Roldan-Tapia L, Parron T, Sanchez F. Neuropsychological effects of long-term exposure to organophosphate pesticides. Neurotoxicol Teratol 2005;259–66.

Safi JM, Abu Mourad TA, Yassin MM. Hematological biomarkers in farm workers exposed to organophosphorus pesticides in the Gaza Strip. Arch Environ Occup Health 2005;60(5):235–41.

Srivastava AK, Gupta BN, Bihari V, Mathur N, Srivastava LP, Pangtey BS, et al. Clinical biochemical and neurobehavioral studies of workers engages in the manufacture of quinalphos. Food Chem Toxicol 2000;38:65–9.

Stallones L, Beseler C. Pesticide illness, farm practices and neurological symptoms among farm residents in Colorado. Environ Res 2002;90:89–97.

Stefanidou M, Athanaselis S, Velonakis M, Pappa F, Koutselinis A. Occupational exposure to cholinesterase inhibiting pesticides: a Greek case. Int J Environ Health Res 2003;13:23–9.

von Osten RJ, Epomex C, Tinoco-Ojanguren R, Soares AM, Guilhermino L. Effect of pesticide exposure on acetylcholinesterase activity in subsistence farmers from Campeche, Mexico. Arch Environ Health 2004;59(8):418–25.

Weber H. Quick and simple ultra-micro-method for the determination of cholinesterase. Dtsch Med Weschr 1966;91:1927–32.

WHO. Physical status: the use and interpretation of anthropometry. World Health Organ Tech Rep Ser 1995;854:1–452.

Acute Pesticide-Related Illnesses Among Working Youths, 1988–1999

Geoffrey M. Calvert, MD, MPH, Louise N. Mehler, MD, PhD, Rachel Rosales, MSHP, Lynden Baum, MS, Catherine Thomsen, MPH, Dorilee Male, BS, Omar Shafey, PhD, MPH, Rupali Das, MD, MPH, Michelle Lackovic, MPH, and Ernest Arvizu, BA

Objectives. The goal of this study was to describe acute occupational pesticide-related illnesses among youths and to provide prevention recommendations.

Methods. Survey data from 8 states and from poison control center data were analyzed. Illness incidence rates and incidence rate ratios were calculated.

Results. A total of 531 youths were identified with acute occupational pesticide-related illnesses. Insecticides were responsible for most of these illnesses (68%), most of which were of minor severity (79%). The average annual incidence rate among youths aged 15 to 17 years was 20.4 per billion hours worked, and the incidence rate ratio among youths vs adults was 1.71 (95% confidence interval = 1.53, 1.91).

Conclusions. The present findings suggest the need for greater efforts to prevent acute occupational pesticide-related illnesses among adolescents. (*Am J Public Health.* 2003;93:605–610)

Work is a common aspect of youths' lives. In fact, the vast majority of young people are, at some time, employed while they are in school. Many of the hazards faced by working youths are receiving increasing attention.[1–3] Although concerns have been raised about pesticide exposures among working youths,[2,4,5] few data are available to support these concerns.

To address the need for more information about the effects of occupational pesticide exposures among young people, we examined the magnitude, incidence, and nature of acute pesticide-related illnesses among working youths. We also compared the rate of such illnesses among youths with the corresponding rate for adults. In this article, in addition to describing the results of our analyses, we provide recommendations for prevention of these illnesses. To our knowledge, ours is the first study to provide population-based estimates of the occurrence of acute occupational pesticide-related illness among young people.

METHODS

Data were obtained on individuals 17 years or younger who developed acute pesticide-related illnesses while working. We excluded cases involving nonoccupational exposures, attempted suicides, intentional malicious use (e.g., attempted homicide), or exposure for a psychotropic effect. In addition, cases caused by disinfectants were excluded, because such cases are not tracked in many states.

Information on cases was provided by the Toxic Exposure Surveillance System (TESS), the California Department of Pesticide Regulation, the California Department of Health Services, the Texas Department of Health, the Washington State Department of Health, the Oregon Department of Human Services, the New York State Department of Health, the Florida Department of Health, the Louisiana Department of Health and Hospitals, and the Arizona Department of Health Services. TESS, maintained by the American Association of Poison Control Centers, collects poisoning reports submitted by approximately 85% of US poison control centers.[6]

Each of the state agencies that contributed data on cases maintains its own surveillance system for acute pesticide-related illness and injury. It should be noted that 4 states neither have poison control centers that participate in TESS nor have in place a state-based surveillance system (Maine, Mississippi, South Carolina, and Vermont).

The periods for which acute pesticide-related illness and injury surveillance data were available varied by agency. TESS data were available for 1993 through 1998. Surveillance data from Texas are considered complete as of 1987; Oregon, as of 1988; New York and Washington State, as of 1991; Arizona and Louisiana, as of 1992; Florida, as of 1998; and California, as of 1989. Data from state agencies were collected through 1999.

The information collected by TESS and the state agencies includes date of illness, information on the ill individual (sex, age, signs, and symptoms), whether the illness occurred as a result of workplace exposures, and the pesticide or pesticides that produced the illness. Additional information collected by the state agencies but not by TESS includes race/ethnicity, occupation, industry, activity of the individual during the exposure, type of exposure (e.g., drift, direct spray, or exposure to a spill or leaking container), and whether personal protective equipment was used. For the present analysis, we defined use of personal protective equipment as use of goggles, face shields, gloves, or respirators.

The Environmental Protection Agency (EPA) acute toxicity category was sought for all pesticides responsible for illness. EPA classifies pesticide products into 1 of 4 acute toxicity categories based on established criteria. Pesticides having the highest toxicity are placed in category I, and those having the lowest are included in category IV. In the case of the present analyses, the acute toxicity category of the pesticide product responsible for causing an illness was often provided by the contributing state agency. When not provided, information on acute toxicity category was retrieved from a data set made available by EPA.

Information on illness severity was sought for all eligible cases. Except for Washington State and Louisiana, state agencies did not determine severity levels for the cases they identified. TESS criteria were used to assign

ED_001854_00010732-00001

severity levels to the cases provided by TESS and the other state agencies.[6] *Minor effects* consisted of minimally bothersome health effects that generally resolved rapidly. *Moderate effects* consisted of non–life-threatening health effects that were more pronounced or prolonged than minor effects or of a systemic nature. *Major effects* consisted of life-threatening health effects or those resulting in "significant residual disability or disfigurement."

To avoid repeated inclusion of the same case, we compared cases provided by each state agency with cases included in TESS. Cases that matched each other in terms of year and state of exposure, age, sex, and pesticide active ingredient were assumed to involve the same individual. Such individuals were included in the state agency totals only.

Case Definition

Cases were included only if health effects developed subsequent to pesticide contact and these effects were evaluated by poison control or state surveillance professionals as consistent with the known toxicology of the pesticide product. TESS relies on the experience and judgment of poison control center specialists managing specific cases to determine whether the affected individuals have symptoms and signs consistent with the pesticide exposure. No standardized criteria are used to make this determination. A full description of the standardized case definition used by each state agency is beyond the scope of the present article, but this information is available elsewhere.[7]

Data Analysis

SAS software (SAS Institute Inc, Cary, NC) was used for data management and in conducting χ^2 analyses to examine categorical data. Incidence rates among subjects aged 15 to 17 years were calculated for the period 1993 through 1998. The numerator was the total number of illness cases; the denominator was obtained from estimates of hours worked derived from the 1993 through 1998 administrations of the Current Population Survey.[8,9] The Current Population Survey does not provide data on workers younger than 15 years. In calculating incidence rates for young workers, it is preferable to use hours worked rather than employment counts.[9] The reason is that youths work fewer hours per week, and fewer weeks per year, than adults. Using employment counts would underestimate the risk of acute pesticide-related illnesses among young people.

Average annual incidence rates were calculated for young people employed in agricultural (Bureau of the Census industry codes 010–030) and nonagricultural (all other Census Bureau industry codes) industries. Because information on industry was not available from TESS, the assumption was made that the proportion of TESS cases involving individuals employed in agriculture was equal to the proportion found among the cases reported by state agencies. Male and female incidence rates and rates for each of 4 US regional areas were also calculated.

We calculated risks of acute pesticide-related illness among individuals aged 15 to 17 years by comparing rates among these youths with those among adults aged 25 to 44 years.[10] The data on adults were obtained from the same agencies that provided the data on youths, with the same exclusions applied. The age range of the adult comparison group was chosen a priori and was based on methodology used previously in examinations of occupational fatalities.[11] We calculated the incidence rate ratio as the youth–adult ratio of number of acute pesticide-related illnesses per hour worked. A ratio greater than 1 would suggest that youths have a higher risk of acute pesticide-related illnesses than adults. Confidence intervals (CIs) were calculated according to methods described by Rothman.[10]

RESULTS

During 1988 to 1999, 531 youths were identified with acute occupational pesticide-related illnesses. Of these individuals, 428 were identified by TESS and 103 by state agencies (9 cases were identified by both TESS and a state agency). The median age among these young people was 16 years (range: 6–17 years), and 122 (23%) were 13 years or younger; 68% were male. Information on race and ethnicity was available for 42 of the patients identified by state agencies (TESS does not collect this information). All 42 were White, and 21 of these individuals (51%) also reported Hispanic ethnicity. Of the 524 cases for which month of illness was known, 368 (70%) occurred between May and August.

Between 1993 and 1998, the average annual incidence rate among youths aged 15 to 17 years was 20.4 per billion hours worked (Table 1). Incidence rates have decreased in recent years (Table 2). The incidence rate was much higher among those employed in agriculture (196.9/billion hours worked) than among those not so employed (7.0/billion hours worked), and the rate was higher among male (27.9/billion hours worked) than among female (11.5/billion hours worked) youths. The rate was highest among those working in Western-region states (Table 3).

The risk of acute occupational pesticide-related illness was higher in youths than in adults (Tables 1 and 2). Overall, the incidence rate ratio among working youths compared with adults was 1.71; the ratio was lower among young people employed in agriculture (0.74). Results showed that incidence rate ratios were highest in the Midwest and lowest in the West (Table 3).

Information on the pesticides responsible for illnesses is provided in Table 4. Insecticides were responsible for 68% of the illnesses. Among the insecticides, organophosphates (142 cases) and pyrethroids (57 cases) were most commonly responsible. Specific organophosphate insecticides included chlorpyrifos (40 cases), diazinon (23 cases), and malathion (12 cases). Among the specific pyrethroids associated with illnesses were cypermethrin (14 cases) and cyhalothrin (12 cases). Glyphosate (33 cases) and 2,4-dichlorophenoxyacetic acid (16 cases) were the specific herbicides most commonly associated with youth illnesses.

Information on EPA acute toxicity category was available for 432 (81%) of the affected individuals. Of these youths, 51 (12%) were exposed to acute toxicity category I pesticides, 90 (21%) were exposed to category II pesticides, and 291 (67%) were exposed to category III pesticides. The percentage of individuals exposed to category I and category II pesticides was higher among those employed in agricultural industries (67%; 44 of 66 cases) than among those employed in nonagricultural industries (41%; 12 of 29 cases; $P=.02$).

ED_001854_00010732-00002

TABLE 1—Total Numbers of Cases of Acute Occupational Pesticide-Related Illness, Estimates of Hours Worked, Incidence Rates, and Incidence Rate Ratios, by Industrial Sector, 1993–1998

	Working Youths Aged 15–17 Years			Working Adults Aged 25–44 Years			
Industrial Sector (Bureau of the Census Codes)	No. (%) With Acute Occupational Pesticide-Related Illnesses	Estimated Total No. of Hours Worked[a]	Incidence Rate[b]	No. (%) With Acute Occupational Pesticide-Related Illnesses	Estimated Total No. of Hours Worked[a]	Incidence Rate[b]	Incidence Rate Ratio (95% Confidence Interval)[c]
All	333 (100)	16 328	20.4	9599 (100)	804 785	11.9	1.71 (1.53, 1.91)
Agriculture (010–030)	213 (64)[d]	1 082	196.9	5367 (56)	20 261	264.9	0.74 (0.65, 0.85)
Nonagriculture (all other codes)	107 (32)[d]	15 246	7.0	4232 (44)	784 524	5.4	1.30 (1.07, 1.58)

[a]In millions of hours.
[b]Per billion hours worked.
[c]Compares the risk of an acute occupational pesticide-related illness among working youths with that among adults in the same industrial sector.
[d]A total of 4% of working youths had no information on industry, and these individuals were not included in analyses stratified by industrial sector.

TABLE 2—Numbers of Cases of Acute Occupational Pesticide-Related Illness, Estimates of Hours Worked, Incidence Rates, and Incidence Rate Ratios, by Year, 1993–1998

	Working Youths Aged 15–17 Years			Working Adults Aged 25–44 Years			
Year	No. With Acute Occupational Pesticide-Related Illnesses	Estimated Total No. of Hours Worked[a]	Incidence Rate[b]	No. With Acute Occupational Pesticide-Related Illnesses	Estimated Total No. of Hours Worked[a]	Incidence Rate[b]	Incidence Rate Ratio (95% Confidence Interval)[c]
1993	46	2 366	19.4	1504	133 066	11.3	1.72 (1.28, 2.31)
1994	51	2 636	19.3	1571	131 774	11.9	1.62 (1.23, 2.14)
1995	74	2 752	26.9	1809	132 993	13.6	1.98 (1.57, 2.50)
1996	60	2 794	21.5	1697	134 419	12.6	1.71 (1.32, 2.21)
1997	49	2 800	17.5	1535	136 483	11.2	1.56 (1.17, 2.07)
1998	53	2 980	17.8	1483	136 050	10.9	1.63 (1.24, 2.14)
Total	333	16 328	20.4	9599	804 785	11.9	1.71 (1.53, 1.91)

[a]In millions of hours.
[b]Per billion hours worked.
[c]Compares the risk of an acute occupational pesticide-related illness among working youths with that among working adults.

Most of the cases of acute occupational pesticide-related illness among youths were of minor severity (418 of 531; 79%). Severity was moderate in 20% of the cases and major in 1% (Table 4). No fatalities were identified. Proportions of cases within a given severity category were similar across the pesticide functional classes (P=.48) and EPA acute toxicity categories (P=.38). A total of 236 (44%) patients were evaluated and treated in a health care facility; 13 (3%) were hospitalized, 5 of whom were treated in an intensive care unit. When all pesticides were combined, the most commonly observed effects involved the gastrointestinal system (28% of youths reported health effects involving this system), followed by dermal effects (23%).

We also identified job tasks associated with illness. Seventy-one percent of subjects (70 of 99) were employed in agriculture (industry and occupation were available for only 99 of the cases identified by state agencies and for none of the TESS cases). Of the 70 agricultural workers affected, 15 (21%) were exposed while directly handling pesticides (i.e., applying [n=13], disposing of [n=1], or mixing and loading [n=1] pesticides), and 55 (79%) were exposed while doing routine work that did not involve direct handling of pesticides.

Only 3 youths appeared to be working in violation of the Fair Labor Standards Act (FLSA). These 3 youths were younger than 16 years, were employed on farms not owned or operated by their parents, and were applying or handling EPA acute toxicity category I or II pesticides. Among the 55 agricultural workers not handling pesticides, 33 (60%) were exposed while handling plant products previously sprayed with pesticides, 9 (16%) were exposed to drift from pesticides applied to the fields where they

ED_001854_00010732-00003

TABLE 3—Numbers of Cases of Acute Occupational Pesticide-Related Illness, Estimates of Hours Worked, Incidence Rates, and Incidence Rate Ratios, by US Region, 1993–1998

	Working Youths Aged 15–17 Years			Working Adults Aged 25–44 Years			
US Region	No. With Acute Occupational Pesticide-Related Illnesses	Estimated Total No. of Hours Worked[e]	Incidence Rate[f]	No. With Acute Occupational Pesticide-Related Illnesses	Estimated Total No. of Hours Worked[e]	Incidence Rate[f]	Incidence Rate Ratio (95% Confidence Interval)[g]
Midwest[a]	89	5 220	17.0	1167	194 783	6.0	2.83 (2.28, 3.51)
Northeast[b]	28	2 589	10.8	938	150 048	6.3	1.71 (0.93, 3.16)
South[c]	125	5 379	23.2	2743	284 187	9.7	2.39 (2.00, 2.86)
West[d]	88	3 140	28.0	4688	175 767	26.7	1.05 (0.66, 1.66)
Total[h]	333	16 328	20.4	9599	804 785	11.9	1.71 (1.53, 1.91)

[a]Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, Wisconsin.
[b]Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont.
[c]Alabama, Arkansas, Delaware, District of Columbia, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, West Virginia.
[d]Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming.
[e]In millions of hours.
[f]Per billion hours worked.
[g]Compares the risk of an acute occupational pesticide-related illness among working youths with that among working adults.
[h]The sum of the number with acute pesticide-related illnesses is less than the total because 3 youths and 63 adults had no information on state of residence.

TABLE 4—Numbers of Youths With Acute Occupational Pesticide-Related Illnesses, by Functional Class of Pesticides and Severity, 1988–1999

Pesticide Functional Class	Minor Severity, No. (%)	Moderate Severity, No. (%)	Major Severity, No. (%)	Total, No. (%)
Insecticides	286 (80)	68 (19)	5 (1)	359 (68)
Herbicides	89 (78)	23 (20)	2 (2)	114 (21)
Fungicides	16 (73)	6 (27)	0 (0)	22 (4)
Insect and moth repellents	15 (79)	4 (21)	0 (0)	19 (4)
Fumigants	7 (70)	3 (30)	0 (0)	10 (2)
Rodenticides	5 (71)	2 (29)	0 (0)	7 (1)
Total	418 (79)	106 (20)	7 (1)	531 (100)

worked, and 8 (15%) were exposed to off-target drift from pesticides applied to neighboring fields.

The remaining 29 youths were not employed in agriculture. Five (17%) of these youths were applying pesticides at the time they were exposed, and they were employed as general laborers or in maintenance, suggesting that pesticide application was not their primary job activity. An additional 12 (41%) youths were employed as clerks or stock workers in the retail sector. Three of these young people were exposed while cleaning up pesticides that had spilled from a store shelf, and one was exposed while changing a canister in an automatic insecticide dispenser. The remaining 13 (45%) youths were employed in a variety of sectors.

Information on use of personal protective equipment was available for only 70 (68%) of the 103 cases reported by state agencies. Such equipment was used by 16% of the youths involved in these episodes. Proportions of young people using protective equipment did not differ significantly according to EPA acute toxicity category ($P=.59$). Nineteen percent (9 of 48) of youths employed in agriculture used protective equipment, as compared with 10% (2 of 21) of youths employed elsewhere ($P=.34$). Only 25% of those who directly handled pesticides used personal protective equipment.

DISCUSSION

The higher risks of acute occupational pesticide-related illnesses among youths than adults observed in this study suggests that current regulations may offer insufficient protection for working youths. There are several potential explanations for these higher risks. Young people are generally less experienced and assertive than adults, and thus they may not question assignments that place them at risk for pesticide exposure.[2] Youths also are often involved in part-time and seasonal work and, as a result, may receive less training. In addition, they may be more sensitive to pesticide toxicity and may manifest acute illnesses at lower exposure thresholds.[12] Because these acute illnesses affect young people at a time before they have reached full developmental maturation, there is also concern about unique and persistent chronic effects.

Youths employed in agriculture appear to have far greater incidence rates of acute occupational pesticide-related illnesses than youths employed elsewhere. These higher rates may be partly explained by the high usage of pesticides in the agriculture industry. In 1996–1997, the agriculture industry used 77% of the total US volume of active pesticide ingredients.[13] In contrast, agricultural employment was responsible for only 7% of total hours

ED_001854_00010732-00004

worked by individuals aged 15 to 17 years (Table 1).

The risk of pesticide poisoning in the agricultural sector was lower among youths than among adults. However, this risk comparison and the others provided should be interpreted with caution, because they represent crude estimates. For example, in terms of our denominator, we do not know how many of the hours worked involved pesticide exposure. We assumed that adults and young people have the same probability of pesticide exposure per hour worked. Unfortunately, we have no data to support or refute this assumption, because the number of pesticide-exposed workers and the duration of their exposure are unknown. This lack of information also precludes our identifying the specific industries and occupations involving the greatest risks.

Among the 99 youths for whom information was available on industry, occupation, and activity at the time of pesticide exposure, only 3 appeared to be working in violation of the FLSA. On the basis of this finding that 97% of the young people affected were engaged in legal activities under the FLSA, we recommend that the act be strengthened to prevent such acute illnesses. According to the FLSA, 16 years is the minimum age at which individuals can be employed in an agricultural job that involves handling or applying acutely toxic agricultural chemicals. Exempted from these prohibitions are youths younger than 16 years who are employed by and working on farms owned or operated by a parent or guardian. In addition, youths are not explicitly prohibited from nonagricultural employment that involves handling or applying pesticides.

To protect young farmworkers, the Worker Protection Standard may also need to be strengthened and better enforced. Among the provisions of this standard are restrictions on individuals' entering a pesticide-treated field before expiration of the restricted entry interval (the period required to elapse before one can reenter a field without personal protective equipment) and requirements for training of workers on the hazards associated with pesticides. We found that among the ill youths employed in the agricultural industry, 33 were exposed through contact with treated surfaces, most commonly by entering farm fields recently sprayed with pesticides (n=30). Three of these cases resulted from violations of restricted entry interval requirements, whereas 18 cases occurred despite compliance with these requirements; this latter finding suggests that longer intervals may be required to protect youths. The unique susceptibility of children was not considered in the establishment of restricted entry intervals. In comparison with adults, young people's greater relative body surface area to body mass ratio can lead to more absorption of pesticides.[14]

Our data and analysis involve several potential limitations. The illness rates we observed are probably underestimates, because a large number of cases among youths are not ascertained. Many cases are never identified because the youths affected neither seek medical care nor contact appropriate authorities (e.g., poison control centers). Furthermore, because the signs and symptoms of acute pesticide-related illnesses are not pathognomonic, many youths who seek medical care may not be correctly diagnosed and thus are not classified as having such illnesses.

Although 30 states require reporting of occupational pesticide-related illnesses, many cases, even those occurring among young people who are correctly diagnosed, are not reported.[7] One reason is that only 8 states have surveillance programs for these illnesses, and the fact that 7 of these 8 states are located in the West or South region helps to explain their higher incidence rates. However, even in these 8 states cases are underreported. For example, when we compared state agency and TESS data from these states, only 14% of the TESS cases were also included in the state agency data (i.e., for the years 1993–1998, among those younger than 18 years or aged 25 to 44 years). In the remaining 42 states, only TESS data are available to obtain counts of occupational pesticide-related illnesses.

Reliance on poison control center data can also lead to underascertainment. Because reporting is voluntary, many poisoning cases do not result in calls to the poison control center. The literature suggests that fewer than one third of poisoning cases treated in health care facilities are reported to poison control centers.[15,16] In addition, we found that in states with availability of both TESS data and data from a state agency, TESS identified only 10% of the cases identified by the state agencies (this comparison was made according to the parameters just described).

Finally, we suspect that some working youths may provide misleading information about their age. For example, one individual who became ill after entering a carbofuran-treated field before the expiration of the restricted entry interval initially reported his age as 19 years. Only later did he concede that his true age was 13 years. Therefore, the data we provide should be considered as representing minimum estimates of the true magnitude of the problem.

A related limitation is that incidence rate ratios may be affected by reporting bias if there is differential reporting of cases among youths relative to adults. We found that the elevated risk observed among youths in comparison with adults was confined to cases identified by TESS (incidence relative risk [IRR]=2.18; 95% CI=1.94, 2.45). Among cases reported by state agencies, the rate among youths was similar to that among adults (IRR=0.94; 95% CI=0.71, 1.24). This difference in risk may be due to biased reporting, either to poison control centers (i.e., these centers may be receiving fewer adult reports than child reports) or to state agencies (i.e., the risks observed in the TESS data may be closer to the true values, and state agencies may see greater underreporting of pediatric cases). That there is less underreporting to poison control centers of pediatric poisoning deaths than adult poisoning deaths suggests that TESS may be susceptible to reporting bias.[6] Conversely, the fact that 27% of the pediatric TESS cases occurred among youths younger than 14 years, as compared with only 6% of state agency cases, suggests that state agencies may be hampered in their ability to identify cases among working children.

A final limitation is that information on industry and occupation was not available for TESS cases. Use of different assumptions about the proportion of TESS cases in which the affected individuals are employed in agriculture can lead to different incidence rates by industry. For example, our analysis of youths aged 15 to 17 years who were in-

ED_001854_00010732-00005

cluded in both the TESS and the state agency data (n=9) revealed that 4 (44%) of these young people were employed in agriculture, 3 (33%) were employed in nonagricultural industries, and 2 (22%) had missing employment information. When these percentages were assigned to the TESS cases, the incidence rates for working youths in agricultural and nonagricultural industries were 146.0 and 7.2 per billion hours worked, respectively. These findings suggest that, relative to the incidence rates presented in Table 1, rates may be lower among those employed in agriculture and higher among those employed in nonagricultural industries.

In conclusion, recognizing that many occupational pesticide-related illnesses can be prevented, we offer the following recommendations:

- Improvements in surveillance are needed to overcome the limitations of underreporting. It would be useful if each state conducted surveillance of acute pesticide-related illnesses and injuries.
- The Bureau of Labor Statistics should improve collection of youth employment data, which would provide more accurate denominator data for calculating injury and illness rates.
- Because the signs and symptoms of acute pesticide-related illnesses may be difficult to link to pesticide exposure, health care professionals should be reminded to consider environmental and occupational exposures.
- Information on child labor laws and adolescent occupational hazards should be more effectively disseminated to students, parents, school officials, and employers.
- The FLSA and the Worker Protection Standard should be reviewed and appropriately revised to ensure that workers younger than 18 years are protected against toxic pesticide exposures. ■

About the Authors

Geoffrey M. Calvert is with the Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, Ohio. Louise N. Mehler is with the Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento. Rachel Rosales is with the Department of Environmental Epidemiology and Toxicology, Texas Department of Health, Austin. Lynden Baum is with the Office of Environmental Health and Safety, Washington State Department of Health, Olympia. Catherine Thomsen is with the Office of Disease Prevention and Epidemiology, Oregon Department of Human Services, Portland. Dorilee Male is with the Bureau of Occupational Health, New York State Department of Health, Troy. Omar Shafey is with the Department of Epidemiology and Surveillance Research, American Cancer Society, Atlanta, Ga. Rupali Das is with the Occupational Health Branch, California Department of Health Services, Oakland. Michelle Lackovic is with the Louisiana Department of Health and Hospitals, New Orleans. Ernest Arvizu is with the Arizona Department of Health Services, Phoenix.

Requests for reprints should be sent to Geoffrey M. Calvert, MD, MPH, National Institute for Occupational Safety and Health, 4676 Columbia Pkwy, R-21, Cincinnati, OH 45226 (e-mail: jac6@cdc.gov).

This article was accepted March 30, 2002.

Contributors

G.M. Calvert was the primary author and took the lead on data analysis and writing the article. The remaining authors assisted in data acquisition and interpretation and provided critical revisions of the article.

Acknowledgments

We wish to thank Anne Mardis, MD, for providing the Current Population Survey data, Charles Mueller for his statistical advice and Jerry Blondell, PhD, for providing access to the TESS data.

Human Participant Protection

No protocol approval was needed for this study.

References

1. Castillo DN, Davis L, Wegman DH. Young workers. *Occup Med.* 1999;14:519–536.
2. Institute of Medicine. *Protecting Youth at Work: Health, Safety, and Development of Working Children and Adolescents in the United States.* Washington, DC: National Academy Press; 1998.
3. Pollack SH, Landrigan PJ, Mallino DL. Child labor in 1990: prevalence and health hazards. *Annu Rev Public Health.* 1990;11:359–375.
4. *Fingers to the Bone: United States Failure to Protect Child Farmworkers.* New York, NY: Human Rights Watch; 2000.
5. *Pesticides: Improvements Needed to Ensure the Safety of Farmworkers and Their Children.* Washington, DC: US General Accounting Office; 2000. Publication GAO/RCED-00-40.
6. Litovitz TL, Klein-Schwartz W, Caravati EM, et al. 1998 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med.* 1999;17:435–487.
7. Calvert GM, Sanderson WT, Barnett M, et al. Surveillance of pesticide-related illness and injury in humans. In: Krieger R, ed. *Handbook of Pesticide Toxicology.* 2nd ed. San Diego, Calif: Academic Press Inc; 2001:603–641.
8. *Current Population Survey 1988–1998 Microdata Files.* Washington, DC: Bureau of Labor Statistics; 2001.
9. Ruser JW. Denominator choice in the calculation of workplace fatality rates. *Am J Ind Med.* 1998;33:151–156.
10. Rothman KJ. *Modern Epidemiology.* Boston, Mass: Little, Brown & Co; 1986:164–172.
11. *Report on the Youth Labor Force.* Washington, DC: Bureau of Labor Statistics; 2000.
12. Bruckner JV. Differences in sensitivity of children and adults to chemical toxicity: the NAS panel report. *Regul Toxicol Pharmacol.* 2000;31:280–285.
13. Aspelin AL, Grube AH. *Pesticide Industry Sales and Usage: 1996 and 1997 Market Estimates.* Washington, DC: US Environmental Protection Agency; 1999.
14. Snodgrass WR. Physiological and biochemical differences between children and adults as determinants of toxic response to environmental pollutants. In: Guzelian PS, Henry CJ, Olin SS, eds. *Similarities and Differences Between Children and Adults: Implications for Risk Assessment.* Washington, DC: International Life Sciences Institute Press; 1992:35–42.
15. Veltri JC, McElwee NE, Schumacher MC. Interpretation and uses of data collected in poison control centers in the United States. *Med Toxicol.* 1987;2:389–397.
16. Chafee-Bahamon C, Caplan DL, Lovejoy FH. Patterns in hospitals' use of a regional poison information center. *Am J Public Health.* 1983;73:396–400.

ED_001854_00010732-00006

NIH Public Access
Author Manuscript
Ann N Y Acad Sci. Author manuscript; available in PMC 2008 July 21.

Published in final edited form as:
Ann N Y Acad Sci. 2008 March ; 1124: 111–126.

The Adolescent Brain

B.J. Casey[a], **Rebecca M. Jones**[a], and **Todd A. Hare**[b]

a *Sackler Institute, Weill Medical College of Cornell University, New York, New York, USA*

b *California Institute of Technology, Pasadena, California, USA*

Abstract

Adolescence is a developmental period characterized by suboptimal decisions and actions that are associated with an increased incidence of unintentional injuries, violence, substance abuse, unintended pregnancy, and sexually transmitted diseases. Traditional neurobiological and cognitive explanations for adolescent behavior have failed to account for the nonlinear changes in behavior observed during adolescence, relative to both childhood and adulthood. This review provides a biologically plausible model of the neural mechanisms underlying these nonlinear changes in behavior. We provide evidence from recent human brain imaging and animal studies that there is a heightened responsiveness to incentives and socioemotional contexts during this time, when impulse control is still relatively immature. These findings suggest differential development of bottom-up limbic systems, implicated in incentive and emotional processing, to top-down control systems during adolescence as compared to childhood and adulthood. This developmental pattern may be exacerbated in those adolescents prone to emotional reactivity, increasing the likelihood of poor outcomes.

Keywords

adolescence; prefrontal cortex; nucleus accumbens; amygdala; limbic; impulsivity; reward; development; risk taking; emotion

Introduction

Adolescence is the period between childhood and adulthood encompassed by changes in physical, psychological, and social development (Ernst et al. 2006). These alterations make this period a time of vulnerability and adjustment (Steinberg 2005). According to the National Center for Health Statistics, there are over 13,000 adolescent deaths in the United States each year. Approximately 70% of these deaths result from motor vehicle crashes, unintentional injuries, homicide, and suicide (Eaton et al. 2006). Results from the 2005 National Youth Risk Behavior Survey (YRBS) show that adolescents engage in behaviors that increase their likelihood of death or illness by driving a vehicle after drinking or without a seat belt, carrying weapons, using illegal substances, and engaging in unprotected sex resulting in unintended pregnancies and STDs, including HIV infection (Eaton et al. 2006). These statistics underscore the importance of understanding risky choices and behavior in adolescents.

Address for correspondence: BJ Casey, Sackler Institute, Weill Cornell Medical College, 1300 York Avenue, Box 140, New York, NY 10021, Voice: +212-746-5832 fax: 212-746-5755 USA. bjc2002@med.cornell.edu.

Conflict of Interests
The authors declare no conflicts of interest.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Adolescence is also a time of increased emotional reactivity. During this period, the social environment is changing such that more time is spent with peers versus adults, and more conflicts arise between the adolescent and his/her parents (Csikszentmihalyi et al. 1977; Steinberg 1989). These changes in social interactions may influence the rise of emotional reactivity. In addition, given the increase in risky choices and behavior during adolescence, it appears the value of positive and negative information may be exaggerated. Greater emotional reactivity and sensitivity during adolescence may play a role in the higher incidence of affective disorder onset and addiction during this developmental period (Pine et al. 2001; Silveri et al. 2004; Steinberg 2005).

A number of cognitive and neurobiological hypotheses have been postulated to explain why adolescents engage in suboptimal choice behavior. In a recent review of the literature on human adolescent brain development, Yurgelun-Todd (2007) suggests that cognitive development during adolescence is associated with progressively greater efficiency of cognitive control and affective modulation. An increase in activity in the prefrontal regions as an indication of maturation (Rubia et al. 2000; Rubia et al. 2006; Tamm et al. 2002) and diminished activity in irrelevant brain regions (Brown et al. 2005; Durston et al. 2006; Monk et al. 2003) are described as the neurobiological explanation for the behavioral changes associated with adolescence. This general pattern, of improved cognitive control and emotion regulation with maturation of the prefrontal cortex, suggests a linear increase in development from childhood to adulthood.

As evidenced by the National Center for Health Statistics on adolescent behavior and mortality, suboptimal choices and actions observed during adolescence represent a nonlinear change in behavior, distinct from childhood and adulthood. If immaturity of prefrontal cortex were the basis for suboptimal choice behavior and heightened emotional reactivity in adolescence, then children who have less developed prefrontal cortex and cognitive abilities should look remarkably similar or even worse than adolescents. Thus, immature prefrontal function alone cannot account for adolescent behavior.

This review will provide evidence from developmental animal and human neuroimaging studies that may account for nonlinear changes in behavior and development during adolescence. A model of adolescent brain development is presented in the context of risk factors including suboptimal decision making and heightened emotional reactivity.

Development of Goal-directed Behavior: Risk versus Impulse

An accurate conceptualization of cognitive and neurobiological changes during adolescence must treat adolescence as a transitional developmental period (Spear 2000), rather than a single snapshot in time (Casey et al. 2005). In other words, to understand this developmental period, transitions into and out of adolescence are necessary for distinguishing distinct attributes of this stage of development. Adolescent behavior has been described as impulsive and risky, almost synonymously, yet these behaviors rely on different cognitive and neural processes (Casey et al. in press), which suggest distinct constructs with different developmental trajectories.

A cornerstone of cognitive development is the ability to suppress inappropriate thoughts and actions in favor of goal-directed ones, especially in the presence of compelling incentives (Casey et al. 2005; Casey et al. 2000; Casey et al. 2002). A number of classic developmental studies have shown that this ability develops throughout childhood and adolescence (Case 1972; Flavell et al. 1966; Keating & Bobbitt 1978; Pascual-Leone 1970). Several theorists (e.g., Bjorkland 1985, 1987; Case 1985) have argued that cognitive development is due to increases in processing speed and efficiency and not due to an increase in mental capacity. Other theorists have included the construct of "inhibitory" processes in their account of cognitive development (Harnishfeger & Bjorkland 1993). According to this account, immature

ED_001854_00010733-00002

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

cognition is characterized by susceptibility to interference from competing sources that must be suppressed (e.g., Brainerd & Reyna 1993; Dempster 1993) (Casey et al. 2002; Diamond 1985; Munakata & Yerys 2001). Thus goal-directed behavior requires the control of impulses or delay of gratification for optimization of outcomes, and this ability appears to mature across childhood and adolescence.

On a cognitive or behavioral level, the immature cognition of adolescence is characterized as impulsive (i.e., lacking cognitive control) and risk taking, with these constructs used synonymously and without appreciation for distinct developmental trajectories for each. Human imaging and animal studies suggest distinct neurobiological and developmental trajectories for the neural systems that underlie these separate constructs of impulse control and risky decisions. Specifically, a review of the literature suggests that impulsivity diminishes with age across childhood and adolescence (Casey et al. 2005; Casey et al. 2002; Galvan et al. 2007) and is associated with protracted development of the prefrontal cortex (Casey et al. 2005; Casey et al. 2002; Galvan et al. 2007) and is associated with protracted development of the prefrontal cortex (Casey et al. 2005). However, there are individual differences in the degree of impulsivity, regardless of age.

In contrast to the linear increase with age associated with impulse control, risk taking appears greater during adolescence relative to childhood and adulthood and is associated with subcortical systems known to be involved in evaluation of incentives and affective information. Human imaging studies that are reviewed here suggest an increase in subcortical activation (accumbens and amygdala) when making risky choices and processing emotional information (Ernst et al. 2005; Monk et al. 2003; Montague & Berns 2002) (Kuhnen & Knutson 2005; Matthews et al. 2004) that is exaggerated in adolescents, relative to children and adults (Ernst et al. 2005; Galvan et al. 2006).

These findings suggest distinct neurobiological trajectories for impulse versus risk taking behavior. The limbic subcortical systems appear to be developed by adolescence in contrast to control systems that show a protracted and linear developmental course into young adulthood. The prefrontal cortical control systems are necessary for overriding inappropriate choices and actions in favor of goal-directed ones.

Animal Studies of Adolescent Brain Development

Until recently, much of our understanding of the adolescent brain has come from animal studies. These experiments have been critical for obtaining information about the neurochemical and cellular changes that occur as a function of age. The validity of animal models to study adolescence has been questioned, since it is argued that only humans undergo the psychological stress of adolescence (e.g., Bogin 1994). However, animals including rodents and nonhuman primates exhibit increased social interactions during adolescence (Primus & Kellogg 1989) as well as novelty-seeking and risk-taking behaviors (Adriani et al. 1998; Spear 2000). These behavioral findings suggest that animal models are appropriate for studying neurobiological changes during adolescence.

Studies in rodents have shown at the cellular level that there are distinct changes in limbic and prefrontal regions during adolescence. During early puberty, there is an overproduction of axons and synapses, followed by rapid pruning in later adolescence (Crews et al. 2007). Specifically, there is dendritic pruning in the amygdala (Zehr et al. 2006), nucleus accumbens (Teicher et al. 1995), and prefrontal cortex (Andersen & Teicher 2004; Andersen et al. 2000) and continual growth in the density of the fibers connecting the amygdala and prefrontal cortex into early adulthood (Cunningham et al. 2002). There is more prolonged pruning throughout adolescence in the prefrontal cortex versus the accumbens (Andersen et al. 2000; Teicher et

ED_001854_00010733-00003

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

al. 1995). These differences in pruning in rodents are consistent with our model suggesting that the accumbens matures earlier than the prefrontal cortex.

Consistent with the cellular changes in animals, there are alterations in neurotransmission in these subcortical and cortical areas. Animal studies have shown that dopamine is crucial for communication between the accumbens, amygdala, and prefrontal cortex and that signaling between these regions relies upon the fine balance between excitatory and inhibitory dopamine transmission (Floresco & Tse 2007; Grace et al. 2007; Jackson et al. 2001). There are significant peaks in dopamine expression during adolescence. Dopamine projections to the prefrontal cortex continue to develop into early adulthood, with dopamine levels peaking in the prefrontal cortex during adolescence versus earlier or later in life in nonhuman primates (Rosenberg & Lewis 1994, 1995) and in rats (Kalsbeek et al. 1988). Dopamine receptor expression is highest in the accumbens during early adolescence (Tarazi et al. 1998). These findings in rodents suggest that there are specific regions undergoing structural changes, and therefore, connections and communication between subcortical and cortical regions are in transition and in flux during adolescence. Significant evidence suggests that the neuroanatomical changes described above are also occurring during adolescence in humans, but our methods for studying humans only provide an approximate index of such changes.

Neuroimaging Studies of Human Brain Development

Our current understanding of the human adolescent brain has come from advances in neuroimaging methodologies that can be used with developing human populations. These methods depend on magnetic resonance imaging (MRI) methods (see Fig. 1) and include structural MRI, which is used to measure the size and shape of structures; diffusion tensor imaging (DTI), which is used to index connectivity of white matter fiber tracts; and functional MRI which is used to measure patterns of brain activity. These methods have furthered our understanding of the neurobiological basis and development of reward or incentive behavior relative to goal-directed behavior.

MRI Studies of Human Brain Development

Several studies have used structural MRI to map the developmental course of the normal brain (for review, see Durston et al. 2001). Although the brain reaches approximately 90% of its adult size by age six, the gray and white matter subcomponents of the brain continue to undergo dynamic changes throughout adolescence. Data from recent longitudinal MRI studies indicate that the change in gray matter volume over time has an inverted U-shape pattern and has greater regional variation than white matter (Giedd 2004; Gogtay et al. 2004, Sowell et al. 2003, 2004). In general, regions that involve primary functions, such as motor and sensory systems, mature earliest compared to the higher-order association areas that integrate these primary functions (Gogtay et al. 2004; Sowell et al. 2004). MRI studies show loss of cortical gray matter first in primary sensorimotor areas, followed by that in the dorsolateral prefrontal and lateral temporal cortices (Gogtay et al. 2004) (see Fig. 2). This pattern of change is consistent with nonhuman primate (Bourgeois et al. 1994) and human postmortem studies (Huttenlocher 1979) indicating that the prefrontal cortex is one of the last brain regions to mature. In contrast to gray matter, white matter volume increases in a roughly linear pattern throughout development and into adulthood (Gogtay et al. 2004). These changes most likely reflect ongoing myelination of axons by oligodendrocytes enhancing neuronal conduction and communication.

When examining neuroanatomical changes across development, the subcortical regions are often overlooked, however, it is important to note that these areas have some of the largest changes during development in the brain, particularly in the basal ganglia (Sowell et al. 1999) and specifically in males (Caviness et al. 1996; Giedd et al. 1996; Reiss et al. 1996).

ED_001854_00010733-00004

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Developmental changes in structural volume within basal ganglia and prefrontal regions are interesting in light of the previously mentioned animal work showing pruning in these regions during adolescence. These processes allow for the fine tuning and strengthening of connections between prefrontal and subcortical regions during development and learning that may correspond to greater cognitive control.

How do these changes in structure relate to differences in cognition? A number of studies have related frontal lobe structural maturation and cognitive function using neuropsychological and cognitive measures (e.g., Sowell et al. 2003). Specifically, these studies showed associations between MRI-based regional volumes of the prefrontal cortex and basal ganglia with measures of cognitive control (i.e., ability to override an inappropriate response in favor of another or to suppress attention toward irrelevant stimulus attribute in favor of relevant stimulus attribute) (Casey et al. 1997, 1997). These findings suggest that cognitive changes are reflected in structural brain changes and underscore the importance of subcortical (basal ganglia) as well as cortical (e.g., prefrontal cortex) development. While these findings showed associations between structure and function, a more in-depth discussion of functional imaging evidence for changes in activity that more directly coincide with behavior across development is presented in the fMRI section.

DTI Studies of Human Brain Development

The MRI-based morphometry studies previously reviewed suggest that during development, cortical connections are fine tuned via elimination of an over-abundance of synapses and by strengthening of relevant connections, although these measures do not have the resolution to visualize or measure synapses. Recent advances in MRI technology, like DTI, provide a potential tool for examining the role of specific white matter tracts in the development of the brain and behavior (for review, see Cascio et al. 2007). Examining white matter tracts can provide knowledge about pathways of connectivity in the brain, and presumably it is via these pathways that information is able to travel from one region of the brain to another (Cascio et al. 2007). Relevant to this paper are the neuroimaging studies that have linked the development of white matter fiber tracts with improvements in cognitive ability with age.

Recently, associations have been shown between DTI-based measures of prefrontal white matter development and cognition in children. Nagy and colleagues showed a positive correlation between maturation of prefrontal–parietal fiber tracts and working memory in children (Nagy et al. 2004), which is consistent with functional neuroimaging studies showing differential recruitment of these regions in children relative to adults. Using a similar approach, Liston and colleagues (2006) have shown that white matter tracts between prefrontal–basal ganglia and posterior fiber tracts continue to develop across childhood into adulthood, but only tracts between the prefrontal cortex and basal ganglia are correlated with impulse control, as measured by performance on a go/no-go task. The prefrontal fiber tracts were defined by regions of interests, which were identified in an fMRI study using the go/no-go task. In developmental DTI studies, fiber tract measures were correlated with age, but specificity of particular fiber tracts with cognitive performance were shown by dissociating the particular tract (Liston et al. 2006) or cognitive ability (Nagy et al. 2004). These findings highlight the importance of examining not only regional, but also related circuitry changes, when making inferences about neural changes in cognition across development.

Functional MRI Studies of Human Brain Development

Compared to MRI and DTI, fMRI is a more direct approach for examining behavior changes during development and for establishing structure–function relationships. Using fMRI to measure functional changes in the developing brain has significant potential for the field of

ED_001854_00010733-00005

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

developmental science and provides a means for constraining interpretations of adolescent behavior.

As stated previously, the development of the prefrontal cortex is believed to play an important role in the maturation of higher cognitive abilities such as decision making and cognitive control (Casey et al. 2002; Casey et al. 1997; Hare & Casey 2005). Many behavioral paradigms, together with fMRI, have assessed the neurobiological basis of these abilities, including flanker, Stroop, and go/no-go tasks (Casey et al. 1997; Casey et al. 2000; Durston et al. 2003). Collectively, these studies show that children recruit distinct but often larger and more diffuse prefrontal regions when performing these tasks than do adults. The patterns of brain activity that are important for task performance, such as those regions that correlate with cognitive performance, become more fine tuned with age. Regions that are not correlated with task performance diminish in activity with age. This pattern has been observed across both cross-sectional (Brown et al. 2005) and longitudinal studies (Durston et al. 2006) and across a variety of paradigms. Neuroimaging studies cannot definitively characterize the mechanism of such developmental changes as dendritic arborization or synaptic pruning. However, these studies suggest that change over a period of time results in both refinement within brain regions as well as fine tuning of projections from these regions (Brown et al. 2005; Bunge et al. 2002; Casey et al. 1997; Casey et al. 2002; Luna et al. 2001; Moses et al. 2002; Schlaggar et al. 2002; Tamm et al. 2002; Thomas et al. 2004; Turkeltaub et al. 2003).

Functional MRI Studies of Behavior during Adolescence

The question remains how can fMRI studies help explain whether adolescents, compared to children or adults, are 1) lacking sufficient cognitive control (impulsive), 2) risky in their choices and actions, and 3) more sensitive to affective information when required to exert cognitive control than children or adults.

Impulse control, as measured by cognitive control tasks like the go/no-go task, shows a linear pattern of development across childhood and adolescence, as described above. However, we were interested in understanding changes across development in top-down control regions and subcortical reward-seeking regions. It is only recently that risk taking in adolescents has been examined with neuroimaging techniques (Ernst et al. 2005; May et al. 2004). These studies have focused primarily on the region of the accumbens, a portion of the basal ganglia involved in predicting reward outcomes. Although two recent reports showed less ventral prefrontal activity (Eshel et al. 2007) and posterior mesofrontal activity (Bjork et al. 2007) in adolescents versus adults on risk-taking behavior, the goal of our studies was to characterize the development of limbic subcortical regions involved in motivation and emotional reactivity in conjunction with top-down control regions (prefrontal cortex). Many studies have examined the neural response in children and adolescents to affective information (e.g., emotional faces) (Baird et al. 1999; Killgore et al. 2001; Monk et al. 2003; Thomas et al. 2001b; Yurgelun-Todd & Killgore 2006) but typically have used passive viewing or attention tasks (Monk et al. 2003) unrelated to processing of the affective information. Our studies examine how affect influences cognitive control across development and characterizes the activation of the subcortical systems (amygdala) involved in affect regulation relative to the cortical (prefrontal) regions associated with cognitive control.

A Neurobiological Model of Adolescence

How do neural changes in subcortical regions (e.g., accumbens and amygdala) associated with reward-seeking and emotion coincide with development of the prefrontal regions and do they relate to impulsivity and risk-taking behaviors? We have developed a neurobiological model of adolescent development within this framework that builds on rodent models (Laviola et al. 1999; Spear 2000) and recent imaging studies of children, adolescents, and adults (Ernst et al.

ED_001854_00010733-00006

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

2005; Galvan et al. 2007; Galvan et al. 2006; Hare & Casey, in press). Figure 3 depicts this model illustrating how bottom-up limbic and prefrontal top-down control regions should be considered together. The graph shows different developmental trajectories for these systems, with limbic systems developing earlier than prefrontal control regions. According to this model, the individual is biased more by functionally mature limbic regions during adolescence (i.e., imbalance of limbic relative to prefrontal control), compared to children, for whom these systems are both still developing, and compared to adults, for whom these systems are fully mature. This perspective provides a basis for nonlinear shifts in behavior across development, due to earlier maturation of this limbic system relative to the less mature top-down prefrontal control region. Furthermore, with development and experience, the functional connectivity between these regions provides a mechanism for top-down control of these regions (Hare & Casey, in press). Our model reconciles the contradiction between health statistics of risky behavior during adolescence and the astute observation by Reyna and Farley (2006) that adolescents are able to reason and understand risks of behaviors in which they engage.

According to our model, in emotionally salient situations, the more mature limbic system will win over the prefrontal control system. In other words, when a poor decision is made in an emotional context, the adolescent may know better, but the salience of the emotional context biases his or her behavior in opposite direction of the optimal action.

Our neurobiological model proposes that the combination of heightened responsiveness to rewards and immaturity in behavioral control areas may bias adolescents to seek immediate rather than long-term gains, perhaps explaining their increase in risky decision making and emotional reactivity. Tracking subcortical (e.g., accumbens and amygdala) and cortical (e.g., prefrontal) development of decision making and emotional reactivity across childhood and through adulthood provides additional clarification on whether changes reported in adolescence are specific to this period of development or, rather, reflect maturation that is steadily occurring in a somewhat linear pattern from childhood to adulthood.

Two recent fMRI studies spanning from childhood to adulthood provide empirical evidence consistent with our neurobiological model. In the first study (Galvan et al. 2006), we examined behavioral and neural responses to reward manipulations across development, focusing on brain regions implicated in reward-related learning and behavior in animal (Hikosaka & Watanabe 2000; Pecina et al. 2003; Schultz 2006) and adult imaging studies (e.g., Knutson et al. 2001; O'Doherty et al. 2001; Zald et al. 2004) and in studies of addiction (Hyman & Malenka 2001; Volkow & Li 2004). Based on rodent models (Laviola et al. 1999; Spear 2000) and previous imaging work (Ernst et al. 2005), we hypothesized that relative to children and adults, adolescents would show exaggerated responses to reward as indexed by elevated accumbens activity in concert with less mature recruitment of top-down prefrontal control regions.

Our findings were consistent with rodent models (Laviola et al. 2003) and previous imaging studies during adolescence (Ernst et al. 2005), which show enhanced accumbens activity to rewards. Adolescents, as compared to children and adults, showed an exaggerated accumbens response in anticipation of reward. However, both children and adolescents showed a less mature response in prefrontal control regions than adults. These findings suggest that there are different developmental trajectories for these regions. The enhancement in accumbens activity during adolescence may relate to the increase in impulsive and risky behaviors observed during this period of development (see Fig. 4).

In the second study, we examined the development of behavioral and neural responses in performance of an emotional go/no-go paradigm (Hare & Casey, in press; Hare et al. 2005). During the experiment, participants were presented with two emotional facial expressions (fearful, neutral, or happy) and were asked to respond to one of the emotions (e.g., fear) and

ED_001854_00010733-00007

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

suppress their response to the other emotion (e.g., neutral). In the context of negative emotional information (fearful faces), reaction times improved with age but were longer when detecting fearful faces relative to a neutral or happy face. This slowing in reaction time was correlated with greater amygdala activity (Hare & Casey, in press). Activity in the orbital frontal cortex increased with age, and greater orbital frontal activity relative to amygdala was associated with more efficiency in suppressing emotional reactivity (longer reaction times and greater amygdala activity). These findings are in accordance with animal studies (Baxter et al. 2000) which show connectivity between the amgydala and orbital frontal cortex are important for assessing changes in emotional value of an object and adapting behavior accordingly.

Differential recruitment of prefrontal and subcortical regions has been reported across a number of developmental fMRI studies (Casey et al. 2002; Monk et al. 2003; Thomas et al. 2004). These findings were typically interpreted in terms of immature prefrontal regions rather than as an imbalance between prefrontal and subcortical regional development. Given evidence of prefrontal regions in guiding appropriate actions in different contexts (Miller & Cohen 2001), immature prefrontal activity might hinder appropriate estimation of future outcomes, especially when making a decision within an emotional context (i.e., heat of the moment). This interpretation is consistent with previous research showing elevated subcortical, relative to cortical, activity when decisions are biased by immediate versus long-term gains (McClure et al. 2004). Further, fMRI studies have shown limbic subcortical activity positively correlates with suboptimal choice behaviors (Kuhnen & Knutson 2005).

In sum, during adolescence, relative to childhood or adulthood, an immature ventral prefrontal cortex may not provide sufficient top-down control of robustly activated reward and affect processing regions (e.g., accumbens and amygdala). This imbalance in development of these regions and relative top-down control results in less influence of prefrontal systems (orbitofrontal cortex) relative to the accumbens and amygdala in reward valuation and emotional reactivity.

Why Would the Adolescent Brain Be Programmed This Way?

Adolescence can be described as a progressive transition from childhood into adulthood with an indefinable ontogenetic time course (Spear 2000) yet often co-occurring with puberty, which is defined by specific biological markers. The significant neuroendocrinological changes associated with puberty, such as increases in adrenal and gonadal hormones, are correlated with the development of secondary sexual characteristics and can influence brain function (for a review see Spear 2000). The onset and hormone fluctuations of puberty may provide an explanation for the observed functional differences in subcortical activity between children and adolescents, versus activity in the prefrontal region, which reflects a linear change with age.

From an evolutionary perspective, adolescence is the period in which independence skills are acquired in order to increase the success of separating from the protective influence of the family. It is also a period when there is an increase in the likelihood of harm such as injury, depression, anxiety, drug use, and addiction (Kelley et al. 2004). However, our neurobiological model suggests that risky behavior and emotional reactivity are the products of a biologically driven imbalance between increased novelty and positive sensation seeking in conjunction with immature "self-regulatory competence" (Steinberg 2004).

As previously mentioned, during adolescence, independence-seeking behaviors are prevalent across species, such as increases in peer-directed social interactions and intensifications in novelty seeking and risk-taking behaviors. In other species such as rodents, nonhuman primates, and birds, behaviors like seeking out same-age peers and fighting with parents are also observed and may be important adaptive skills to remove the adolescent from the home

ED_001854_00010733-00008

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

territory in order to mate (Spear 2000). Relative to adults, periadolescent rats show increased novelty-seeking behaviors in a free-choice novelty paradigm (Laviola et al. 1999). Neurochemical evidence indicates that the balance in the adolescent brain between cortical and subcortical dopamine systems begins to shift toward greater cortical dopamine levels during adolescence (Spear 2000). And as previously described, in the nonhuman primate there is an increase in dopamine enervation of the prefrontal cortex into early adulthood (Rosenberg & Lewis 1995). Thus this elevated risk-taking behavior appears to occur across species and have important adaptive functions.

It is possible that this developmental pattern is an evolutionary feature. One needs to engage in high-risk behavior in order to leave the family and village to find a mate. This risk behavior occurs simultaneously with an increase in sexual hormones, resulting in adolescents seeking sexual partners and is seen in other species. In conjunction with this novelty-seeking behavior, there would need to be some mechanism for detecting cues of safety or danger. The increase in emotional reactivity during this period may allow adolescents to be more vigilant and aware of threat, to ensure their survival as they move from a safe environment to a novel one. In today's society when adolescence may extend indefinitely—with individuals well into their 20s living with their parents, remaining financially dependent, and choosing mates later in life —these behaviors may be deemed inappropriate.

Biological Predispositions, Development, and Risky Behavior

The recognition of individual differences in impulse control and taking risks is not new in the field of psychology (Benthin et al. 1993). Perhaps one of the classic examples of individual differences in the social, cognitive, and developmental psychology literatures is delay of gratification (Mischel et al. 1989). Delay of gratification is typically assessed in 3- to 4-year-old toddlers. A toddler is seated in a room with two cookies and a bell. The child is then told that the experimenter will leave the room in order to prepare for upcoming activities and explains to the child that if she remains in her seat and does not eat a cookie, she will receive the large reward (2 cookies). If the child cannot wait, she should ring a bell to summon the experimenter and thereby receive the smaller reward (1 cookie). Distractions in the room are minimized, with no toys, books, or pictures. The experimenter returns after 15 minutes or after the child has rung the bell, eaten the rewards, or shown any signs of distress. Mischel (1989) showed that children typically behave in one of two ways: 1) either they ring the bell almost immediately in order to have the cookie, which means they only get one; or 2) they wait and optimize their gains to receive both cookies. This observation suggests that some individuals are better than others in their ability to control impulses in the presence of highly salient incentives, and this bias can be detected in early childhood (Mischel et al. 1989). This differential in impulse control appears to remain throughout adolescence and young adulthood (Eigsti et al. 2006).

What might explain individual differences in decision making and behavior? Some theorists have postulated that the dopaminergic mesolimbic circuitry, implicated in reward processing, underlies risky behavior (Blum et al. 2000), and that individual differences in this circuitry might relate to the propensity to engage in risky behavior (O'Doherty 2004). A number of studies have shown increases in activity in the nucleus accumbens immediately prior to making risky choices on monetary-risk paradigms (Kuhnen & Knutson 2005; Matthews et al. 2004; Montague & Berns 2002), and as described previously, adolescents show exaggerated accumbens activity to rewarding outcomes relative to children or adults (Ernst et al. 2005; Galvan et al. 2006). Collectively, these data suggest that as a group adolescents may be more likely to engage in risky choices (Gardener & Steinberg 2005). However, some adolescents will be more prone than others to engage in risky behaviors, putting them at potentially greater risk for negative outcomes. Therefore it is important to consider individual variability when

ED_001854_00010733-00009

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

examining complex brain–behavior relationships related to risk taking and reward processing in developmental populations.

To explore individual differences in risk-taking behavior, Galvan and colleagues (2007) recently examined the association between activity in reward-related neural circuitry in anticipation of a large monetary reward with behavioral measures of risk taking and impulsivity in adolescence. Specifically, Galvan and colleagues used functional magnetic resonance imaging and anonymous self-report rating scales of risky behavior, risk perception, and impulsivity in individuals between the ages of 7 and 29 years (see Fig. 6). There was a positive association between accumbens activity and the likelihood of engaging in risky behavior across development. In other words, those individuals, who perceived risky behaviors as leading to dire consequences, activated the accumbens less to reward. Impulsivity ratings were not associated with accumbens activity, but rather with age, further dissociating impulse control from incentive-based risky behaviors. These findings suggest that during adolescence, some individuals have a predisposition to engage in risky behaviors due to developmental neural changes.

Adolescent behavior is repeatedly characterized as impulsive and risky, yet this review of the imaging literature suggests different neurobiological substrates and developmental trajectories for these two types of behavior. Specifically, impulsivity is associated with immature ventral prefrontal development and gradually diminishes from childhood to adulthood (Casey et al. 2005). The negative correlation between impulsivity ratings and age in the study by Galvan and colleagues (2007) further supports this notion. In contrast, risk taking is associated with an increase in accumbens activity (Kuhnen & Knutson 2005; Matthews et al. 2004; Montague & Berns 2002) that is exaggerated in adolescents, relative to both children and adults (Ernst et al. 2005; Galvan et al. 2006). Thus adolescent choices and behavior cannot be explained by impulsivity or protracted development of the prefrontal cortex alone, as children would then be predicted to be greater risk takers. The findings provide a neural basis for why some adolescents are at greater risk than others, but also demonstrate a basis for why adolescent risk-taking behavior in general is different from risk taking in children and adults.

Adolescence, Individual Differences, and Affective Disorders

Adolescence is a time of greater emotional reactivity and a period when symptoms of many psychiatric disorders (e.g., schizophrenia, depression, anxiety) manifest. Normal adolescent development can be interpreted as the coordination of emotions and behavior in the social and intellectual environment, and the development of psychopathology during adolescence can be seen as resulting from a difficulty in balancing these factors (Steinberg 2005). We have previously described enhanced bottom-up emotional processing in subcortical regions relative to less effective top-down modulation in prefrontal regions to affective information during adolescence. It is possible that this imbalance may play a role in the increased risk for affective disorders during adolescence (Steinberg 2005). Clearly, not all adolescents develop psychopathology; there must be individual variability in emotional reactivity and the ability to modulate these behaviors. Individual differences may predispose a person to be at greater risk for poorer outcomes.

The amygdala has been implicated as a key neural region in emotional dysregulation in psychiatric disorders. This region is essential to learning the emotional significance of cues in the environment (see Maren & Quirk 2004 for review). In animal studies, amygdala lesions result in a reduction of fear behavior (Anglada-Figueroa & Quirk 2005; Davis & Whalen 2001; Kalin et al. 2004), and human neuroimaging studies have shown increases in activity in the amygdala to fearful stimuli in adults (Breiter et al. 1996; Morris et al. 1998) and in children (Thomas et al. 2001b). There is evidence for dysregulation of amygdala activity in anxious and

ED_001854_00010733-00010

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

depressed children (Thomas et al. 2001a) and adults (Leppanen 2006; Rauch et al. 2003; Thomas et al. 2001a).

In a recent study, we examined individual differences in anxiety levels as measured by the Spielberger State Trait Anxiety Index and neural responses to affective information in adolescents and adults during an emotional go/no-go task (Hare et al. in press). Adolescents showed greater initial amygdala activity than adults, and sustained amygdala activity was correlated with trait anxiety. Increased activity in orbitofrontal regions correlated with a decrease in amygdala activity over time (i.e., repeated presentation of a fearful face, see Fig. 7), suggesting dampening of emotional reactivity due to top-down control from prefrontal regions. These findings are consistent with animal studies showing the importance of the orbitofrontal cortex (OFC) in extinction of fear conditioning in animals with repeated exposure to empty threat (Gallagher et al. 1999).

Our results are consistent with previous fMRI studies in clinically anxious adults and children that have shown unregulated amygdala activity to negative emotional information and less activity in the prefrontal cortex (McClure et al. 2007; Shin et al. 2004; Thomas et al. 2001b) in adolescents at risk for anxiety disorders (Perez-Edgar et al. 2007). Together these findings suggest that prefrontal regions serve to regulate emotional reactivity and that individual differences in emotion regulation may be due to an imbalance in activity between these regions that is exacerbated during adolescence.

Conclusions

Human imaging studies show structural and functional changes in frontolimbic regions (Jernigan et al. 1991; Giedd et al. 1999; Giedd et al. 1996; Sowell et al. 1999; for review, Casey et al. 2005; Jernigan et al. 1991; Giedd et al. 1999; Giedd et al. 1996; Sowell et al. 1999) for review, (Casey et al. 2005) that seem to parallel increases in cognitive control and self-regulation (Casey et al. 1997; Luna & Sweeney 2004; Luna et al. 2001; Rubia et al. 2000; Steinberg 2004). These changes appear to show a shift in activation of prefrontal regions from diffuse to more focal recruitment over time (Brown et al. 2005; Bunge et al. 2002; Casey et al. 1997; Durston et al. 2006; Moses et al. 2002) and elevated recruitment of subcortical regions during adolescence (Casey et al. 2002; Durston et al. 2006; Luna et al. 2001). Although neuroimaging studies cannot definitively characterize the mechanism of such developmental changes, these changes in volume and structure may reflect development within, and refinement of, projections to and from these brain regions during maturation suggestive of fine tuning of the system with development.

We have discussed the importance of considering individual variability when examining complex brain–behavior relationships related to risk taking, reward processing, and emotional reactivity in developmental populations. Using an approach that looks at developmental trajectories, rather than snapshots in time, allows one to comprehensively study these behaviors during development and examine individual differences. It is not possible to fully explain the emergence of affective disorders or atypical development by simply examining one time point. Longitudinal studies across development would be the best methodology to address these issues.

Taken together, the findings synthesized here indicate that increased risk-taking behavior and greater emotional reactivity in adolescence are associated with different developmental trajectories of subcortical limbic regions relative cortical control regions. These developmental changes can be exacerbated by individual differences (e.g., genetic risk) in baseline activity of limbic systems.

ED_001854_00010733-00011

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

This model of development reconciles a number of contradictions and myths about adolescence. First, there have been many reports that suggest that adolescent behavior is due to protracted development of prefrontal cortex. However, if this were the case, then children would engage in similar or worse behavior than adolescents. The National Center for Health Statistics on adolescent behavior and mortality shows that suboptimal choices and actions observed during adolescence represent a nonlinear change in behavior, distinct from childhood and adulthood. Adolescents, unlike children, may be in situations (e.g., driving a car) that may put them at greater risk for mortality, but even when taking these conditions into account, there is still a significant elevation of risky behavior in adolescents in comparison to children. Furthermore, experimental studies have shown that when risk is held constant, such as in the appraisal of risky vignettes, children perceive greater risk in hypothetical scenarios than do adolescents (reviewed in Furby & Beyth-Marom 1992). Our neurodevelopmental model provides an explanation for these nonlinear changes in behavior.

Reyna and Farley (2006) have reconciled the second myth by showing that adolescents are able to reason and understand risks of behaviors in which they engage and do not consider themselves invincible. Prior research has also shown that adolescents knowingly engage in risky behavior, and this is often due to influences of feelings, emotions, and peers (Gardener & Steinberg 2005; Steinberg 2004, 2005). The observation that adolescents know that they are engaging in risky behavior is not supported by the sole explanation of a less developed prefrontal cortex. In this context, our model suggests that the adolescent is capable of making rational decisions, but in emotionally charged situations the more mature limbic system will win over the prefrontal control system.

When faced with an immediate personal decision, adolescents will rely less on intellectual capabilities and more on feelings. Nevertheless, when reasoning about a hypothetical, moral dilemma, the adolescent will rely more on logical information (Steinberg 2005). In other words, when a poor decision is made in the heat of the moment, the adolescent may know better, but the salience of the emotional context biases his or her behavior in opposite direction of the optimal action. This work coincides with studies of social cognition showing that adolescents make more rational decisions about hypothetical scenarios versus real-life situations (Sobesky 1983). The environmental context and emotional significance of the decision greatly influence the adolescent (Steinberg 2005).

Our findings and model have significant implications for heated debates on public policy and the treatment of minors in our judicial system. Adolescents show adult levels of intellectual capability earlier than they show evidence of adult levels of impulse control (Reyna & Farley 2006). As such, adolescents may be capable of making informed choices about their future (e.g., terminating a pregnancy) but do not yet have full capacity to override impulses in emotionally charged situations that require decisions in the heat of the moment. Unfortunately, judges, politicians, advocates, and journalists are biased toward drawing a single line between adolescence and adulthood for different purposes under the law that is at odds with developmental cognitive neuroscience (Steinberg et al. in press). Our neurodevelopmental model of adolescence will hopefully help to make strides in moving this single line to multiple lines that consider developmental changes across both context (emotionally charged or not) and time (in the moment or in the future).

Acknowledgements

This work was supported in part by grants from the National Institute of Drug Abuse R01 DA18879 and the National Institute of Mental Health R01 MH73175 and P50 MH62196 to BJC.

ED_001854_00010733-00012

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

References

Adriani W, Chiarotti F, Laviola G. Elevated novelty seeking and peculiar d-amphetamine sensitization in periadolescent mice compared with adult mice. Behav Neurosci 1998;112(5):1152–1166. [PubMed: 9829793]

Andersen SL, Teicher MH. Delayed effects of early stress on hippocampal development. Neuropsychopharmacology 2004;29(11):1988–1993. [PubMed: 15316569]

Andersen SL, Thompson AT, Rutstein M, Hostetter JC, Teicher MH. Dopamine receptor pruning in prefrontal cortex during the periadolescent period in rats. Synapse 2000;37(2):167–169. [PubMed: 10881038]

Anglada-Figueroa D, Quirk GJ. Lesions of the basal amygdala block expression of conditioned fear but not extinction. J Neurosci 2005;25(42):9680–9685. [PubMed: 16237172]

Baird AA, Gruber SA, Fein DA, Maas LC, Steingard RJ, Renshaw PF, et al. Functional magnetic resonance imaging of facial affect recognition in children and adolescents. J Am Acad Child Adolesc Psychiatry 1999;38(2):195–199. [PubMed: 9951219]

Baxter MG, Parker A, Lindner CC, Izquierdo AD, Murray EA. Control of response selection by reinforcer value requires interaction of amygdala and orbital prefrontal cortex. J Neurosci 2000;20(11):4311–4319. [PubMed: 10818166]

Benthin A, Slovic P, Severson H. A psychometric study of adolescent risk perception. J Adolesc 1993;16(2):153–168. [PubMed: 8376640]

Bjork JM, Smith AR, Danube CL, Hommer DW. Developmental differences in posterior mesofrontal cortex recruitment by risky rewards. J Neurosci 2007;27(18):4839–4849. [PubMed: 17475792]

Bjorkland, DF. The role of conceptual knowledge in the development of organization in children's memory. In: Brainerd, CJ.; Pressley, M., editors. Basic Processes in Memory Development: Progress in Cognitive Development Research. New York: Springer-Verlag; 1985. p. 103-142.

Bjorkland DF. How age changes in knowledge base contribute to the development of children's memory: An interpretive review. Developmental Review 1987;7:93–130.

Blum K, Braverman ER, Holder JM, Lubar JF, Monastra VJ, Miller D, et al. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J Psychoactive Drugs 2000;32(Suppl i–iv):1–112.

Bogin B. Adolescence in evolutionary perspective. Acta Paediatr Suppl 1994;406:29–35. [PubMed: 7734808]discussion 36

Bourgeois JP, Goldman-Rakic PS, Rakic P. Synaptogenesis in the prefrontal cortex of rhesus monkeys. Cereb Cortex 1994;4(1):78–96. [PubMed: 8180493]

Brainerd CJ, Reyna VF. Memory independence and memory interference in cognitive development. Psychol Rev 1993;100(1):42–67. [PubMed: 8426881]

Breiter HC, Etcoff NL, Whalen PJ, Kennedy WA, Rauch SL, Buckner RL, et al. Response and habituation of the human amygdala during visual processing of facial expression. Neuron 1996;17(5):875–887. [PubMed: 8938120]

Brown TT, Lugar HM, Coalson RS, Miezin FM, Petersen SE, Schlaggar BL. Developmental changes in human cerebral functional organization for word generation. Cereb Cortex 2005;15(3):275–290. [PubMed: 15297366]

Bunge SA, Dudukovic NM, Thomason ME, Vaidya CJ, Gabrieli JD. Immature frontal lobe contributions to cognitive control in children: evidence from fMRI. Neuron 2002;33(2):301–311. [PubMed: 11804576]

Cascio CJ, Gerig G, Piven J. Diffusion tensor imaging: Application to the study of the developing brain. J Am Acad Child Adolesc Psychiatry 2007;46(2):213–223. [PubMed: 17242625]

Case R. Balidation of a neo-Piagetian capacity construct. Journal of Experimental Child Psychology 1972;14:287–302.

Case, R. Intellectual Development Birth to Adulthood. New York: Academic Press; 1985.

Casey BJ, Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Schubert AB, et al. Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 1997a;36(3):374–383. [PubMed: 9055518]

ED_001854_00010733-00013

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Casey BJ, Galvan A, Hare TA. Changes in cerebral functional organization during cognitive development. Curr Opin Neurobiol 2005a;15(2):239–244. [PubMed: 15831409]

Casey B, Getz S, Galvan A. Developmental Review. in press

Casey BJ, Giedd JN, Thomas KM. Structural and functional brain development and its relation to cognitive development. Biol Psychol 2000a;54(1–3):241–257. [PubMed: 11035225]

Casey BJ, Thomas KM, Davidson MC, Kunz K, Franzen PL. Dissociating striatal and hippocampal function developmentally with a stimulus-response compatibility task. J Neurosci 2002a;22(19): 8647–8652. [PubMed: 12351738]

Casey BJ, Thomas KM, Welsh TF, Badgaiyan RD, Eccard CH, Jennings JR, et al. Dissocaiation of response conflict, attentional selection, and expectancy with functional magnetic resonance imaging. Proc Natl Acad Sci, USA 2000b;97(18):8728–8733. [PubMed: 10900023]

Casey BJ, Tottenham N, Fossella J. Clinical, imaging, lesion, and genetic approaches toward a model of cognitive control. Dev Psychobiol 2002b;40(3):237–254. [PubMed: 11891636]

Casey BJ, Tottenham N, Liston C, Durston S. Imaging the developing brain: what have we learned about cognitive development? Trends in Cognitive Science 2005b;9(3):104–110.

Casey BJ, Trainor RJ, Orendi JL, Schubert AB, Nystrom LE, Giedd JN, et al. A developmental functional MRI study of prefrontal activation during performance of a go-no-go task. Journal of Cognitive Neuroscience 1997b;9:835–847.

Caviness V, Kennedy D, Richelme C, Rademacher J, Filipek P. The human brain age 7–11 years: a volumetric analysis based on magnetic resonance images. Cereb Cortex 1996;6(5):726–736. [PubMed: 8921207]

Crews F, He J, Hodge C. Adolescent cortical development: a critical period of vulnerability for addiction. Pharmacol Biochem Behav 2007;86(2):189–199. [PubMed: 17222895]

Csikszentmihalyi M, Larson R, Prescott S. The ecology of adolescent activity and experience. Journal of Youth and Adolescence 1977;6:281–294.

Cunningham MG, Bhattacharyya S, Benes FM. Amygdalo-cortical sprouting continues into early adulthood: implications for the development of normal and abnormal function during adolescence. J Comp Neurol 2002;453(2):116–130. [PubMed: 12373778]

Davis M, Whalen PJ. The amygdala: vigilance and emotion. Mol Psychiatry 2001;6(1):13–34. [PubMed: 11244481]

Dempster, FN., editor. Resistance to Interference: Developmental Changes in a Basic Processing Mechanism. 1. New York: Springer-Verlag; 1993.

Diamond A. Development of the ability to use recall to guide action, as indicated by infants' performance on AB. Child Development 1985;56:868–883. [PubMed: 4042750]

Durston S, Davidson MC, Thomas KM, Worden MS, Tottenham N, Martinez A, et al. Parametric manipulation of conflict and response competition using rapid mixed-trial event-related fMRI. Neuroimage 2003;20(4):2135–2141. [PubMed: 14683717]

Durston S, Davidson MC, Tottenham N, Galvan A, Spicer J, Fossella JA, et al. A shift from diffuse to focal cortical activity with development. Dev Sci 2006;9(1):1–8. [PubMed: 16445387]

Durston S, Hulshoff HE, Casey BJ, Giedd JN, Buitelaar JK, Van Engeland H. Anatomical MRI of the developing human brain: What have we learned? J Am Acad Child Adolesc Psychiatry 2001;40(9): 1012–1020. [PubMed: 11556624]

Eaton LK, Kinchen S, Ross J, Hawkins J, Harris WA, Lowry R, et al. Youth risk behavior surveillance-United States, 2005, surveillance summaries. Morbidity and Mortality Weekly Report 2006;55(SS5): 1–108. [PubMed: 16410759]

Eigsti IM, Zayas V, Mischel W, Shoda Y, Ayduk O, Dadlani MB, et al. Predicting cognitive control from preschool to late adolescence and young adulthood. Psychol Sci 2006;17(6):478–484. [PubMed: 16771797]

Ernst M, Nelson EE, Jazbec S, McClure EB, Monk CS, Leibenluft E, et al. Amygdala and nucleus accumbens in responses to receipt and omission of gains in adults and adolescents. Neuroimage 2005;25(4):1279–1291. [PubMed: 15850746]

Ernst M, Pine DS, Hardin M. Triadic model of the neurobiology of motivated behavior in adolescence. Psychol Med 2006;36(3):299–312. [PubMed: 16472412]

ED_001854_00010733-00014

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Eshel N, Nelson EE, Blair RJ, Pine DS, Ernst M. Neural substrates of choice selection in adults and adolescents: development of the ventrolateral prefrontal and anterior cingulate cortices. Neuropsychologia 2007;45(6):1270–1279. [PubMed: 17118409]

Flavell JH, Feach DR, Chinsky JM. Spontaneous verbal rehearsal in a memory task as a function of age. Child Development 1966;37:283–299. [PubMed: 5941895]

Floresco SB, Tse MT. Dopaminergic regulation of inhibitory and excitatory transmission in the basolateral amygdala-prefrontal cortical pathway. J Neurosci 2007;27(8):2045–2057. [PubMed: 17314300]

Furby L, Beyth-Marom R. Risk taking in adolescence: A decision-making perspective. Developmental Review 1992;12(1):1–44.

Gallagher M, McMahan RW, Schoenbaum G. Orbitofrontal cortex and representation of incentive value in associative learning. J Neurosci 1999;19(15):6610–6614. [PubMed: 10414988]

Galvan A, Hare T, Voss H, Glover G, Casey BJ. Risk-taking and the adolescent brain: who is at risk? Dev Sci 2007;10(2):F8–F14. [PubMed: 17286837]

Galvan A, Hare TA, Parra CE, Penn J, Voss H, Glover G, et al. Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. J Neurosci 2006;26 (25):6885–6892. [PubMed: 16793895]

Gardener M, Steinberg L. Peer influence on risk taking, risk preference, and risky decision making in adolescence and adulthood: an experimental study. Developmental Psychology 2005;41:625–635. [PubMed: 16060809]

Giedd JN. Structural magnetic resonance imaging of the adolescent brain. Ann N Y Acad Sci 2004;1021:77–85. [PubMed: 15251877]

Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, et al. Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci 1999;2(10):861–863. [PubMed: 10491603]

Giedd JN, Snell JW, Lange N, Rajapakse JC, Casey BJ, Kaysen D, et al. Quantitative magnetic resonance imaging of human brain development: ages 4–18. Cereb Cortex 1996;6:551–560. [PubMed: 8670681]

Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, et al. Dynamic mapping of human cortical development during childhood through early adulthood. Proc Natl Acad Sci U S A 2004;101 (21):8174–8179. [PubMed: 15148381]

Grace AA, Floresco SB, Goto Y, Lodge DJ. Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. Trends Neurosci 2007;30(5):220–227. [PubMed: 17400299]

Hare T, Casey B. Biological Psychiatry. in press

Hare TA, Casey BJ. The neurobiology and development of cognitive and affective control. Cognition, Brain, Behavior 2005;9(3):273–286.

Hare TA, Tottenham N, Davidson MC, Glover GH, Casey BJ. Contributions of amygdala and striatal activity in emotion regulation. Biol Psychiatry 2005;57(6):624–632. [PubMed: 15780849]

Hare TA, Tottenham N, Voss HU, Glover GH, Casey BJ. The adolescent brain and potential risk for anxiety and depression. Biological Psychiatry. in press

Harnishfeger, KK.; Bjorkland, F. The ontogeny of inhibition mechanisms: A renewed approach to cognitive development. In: Howe, ML.; Pasnek, R., editors. Emgering Themes in Cognitive Development. 1. New York: Springer-Verlag; 1993. p. 28-49.

Hikosaka K, Watanabe M. Delay activity of orbital and lateral prefrontal neurons of the monkey varying with different rewards. Cereb Cortex 2000;10(3):263–271. [PubMed: 10731221]

Huttenlocher PR. Synaptic density in human frontal cortex - developmental changes and effects of aging. Brain Res 1979;163(2):195–205. [PubMed: 427544]

Hyman SE, Malenka RC. Addiction and the brain: the neurobiology of compulsion and its persistence. Nat Rev Neurosci 2001;2(10):695–703. [PubMed: 11584307]

Jackson ME, Frost AS, Moghaddam B. Stimulation of prefrontal cortex at physiologically relevant frequencies inhibits dopamine release in the nucleus accumbens. J Neurochem 2001;78(4):920–923. [PubMed: 11520912]

ED_001854_00010733-00015

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Jernigan TL, Zisook S, Heaton RK, Moranville JT, Hesselink JR, Braff DL. Magnetic resonance imaging abnormalities in lenticular nuclei and cerebral cortex in schizophrenia. Arch Gen Psychiatry 1991;48:881–890. [PubMed: 1929757]

Kalin NH, Shelton SE, Davidson RJ. The role of the central nucleus of the amygdala in mediating fear and anxiety in the primate. J Neurosci 2004;24(24):5506–5515. [PubMed: 15201323]

Kalsbeek A, Voorn P, Buijs RM, Pool CW, Uylings HB. Development of the dopaminergic innervation in the prefrontal cortex of the rat. J Comp Neurol 1988;269(1):58–72. [PubMed: 3361004]

Keating DP, Bobbitt BL. Individual and developmental differences in cognitive processing components of mental ability. Child Development 1978;49:155–167.

Kelley AE, Schochet T, Landry CF. Risk taking and novelty seeking in adolescence: introduction to part I. Ann N Y Acad Sci 2004;1021:27–32. [PubMed: 15251871]

Killgore WD, Oki M, Yurgelun-Todd DA. Sex-specific developmental changes in amygdala responses to affective faces. Neuroreport 2001;12(2):427–433. [PubMed: 11209962]

Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J Neurosci 2001;21(16):RC159. [PubMed: 11459880]

Kuhnen CM, Knutson B. The neural basis of financial risk taking. Neuron 2005;47(5):763–770. [PubMed: 16129404]

Laviola G, Adriani W, Terranova ML, Gerra G. Psychobiological risk factors for vulnerability to psychostimulants in human adolescents and animal models. Neurosci Biobehav Rev 1999;23(7):993–1010. [PubMed: 10580313]

Laviola G, Macri S, Morley-Fletcher S, Adriani W. Risk-taking behavior in adolescent mice: psychobiological determinants and early epigenetic influence. Neurosci Biobehav Rev 2003;27(1–2):19–31. [PubMed: 12732220]

Lenroot RK, Giedd JN. Brain development in children and adolescents: insights from anatomical magnetic resonance imaging. Neurosci Biobehav Rev 2006;30(6):718–729. [PubMed: 16887188]

Leppanen JM. Emotional information processing in mood disorders: a review of behavioral and neuroimaging findings. Curr Opin Psychiatry 2006;19(1):34–39. [PubMed: 16612176]

Liston C, Watts R, Tottenham N, Davidson MC, Niogi S, Ulug AM, et al. Frontostriatal microstructure modulates efficient recruitment of cognitive control. Cereb Cortex 2006;16(4):553–560. [PubMed: 16033925]

Luna B, Sweeney JA. The emergence of collaborative brain function: FMRI studies of the development of response inhibition. Ann N Y Acad Sci 2004;1021:296–309. [PubMed: 15251900]

Luna B, Thulborn KR, Munoz DP, Merriam EP, Garver KE, Minshew NJ, et al. Maturation of widely distributed brain function subserves cognitive development. Neuroimage 2001;13(5):786–793. [PubMed: 11304075]

Maren S, Quirk GJ. Neuronal signalling of fear memory. Nat Rev Neurosci 2004;5(11):844–852. [PubMed: 15496862]

Matthews SC, Simmons AN, Lane SD, Paulus MP. Selective activation of the nucleus accumbens during risk-taking decision making. Neuroreport 2004;15(13):2123–2127. [PubMed: 15486494]

May JC, Delgado MR, Dahl RE, Stenger VA, Ryan ND, Fiez JA, et al. Event-related functional magnetic resonance imaging of reward-related brain circuitry in children and adolescents. Biol Psychiatry 2004;55(4):359–366. [PubMed: 14960288]

McClure EB, Monk CS, Nelson EE, Parrish JM, Adler A, Blair RJ, et al. Abnormal attention modulation of fear circuit function in pediatric generalized anxiety disorder. Arch Gen Psychiatry 2007;64(1):97–106. [PubMed: 17199059]

McClure SM, Laibson DI, Loewenstein G, Cohen JD. Separate neural systems value immediate and delayed monetary rewards. Science 2004;306(5695):503–507. [PubMed: 15486304]

Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 2001;24:167–202. [PubMed: 11283309]

Mischel W, Shoda Y, Rodriguez MI. Delay of gratification in children. Science 1989;244(4907):933–938. [PubMed: 2658056]

ED_001854_00010733-00016

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Monk CS, McClure EB, Nelson EE, Zarahn E, Bilder RM, Leibenluft E, et al. Adolescent immaturity in attention-related brain engagement to emotional facial expressions. Neuroimage 2003;20(1):420–428. [PubMed: 14527602]

Montague PR, Berns GS. Neural economics and the biological substrates of valuation. Neuron 2002;36(2):265–284. [PubMed: 12383781]

Morris JS, Friston KJ, Buchel C, Frith CD, Young AW, Calder AJ, et al. A neuromodulatory role for the human amygdala in processing emotional facial expressions. Brain 1998;121(Pt 1):47–57. [PubMed: 9549487]

Moses P, Roe K, Buxton RB, Wong EC, Frank LR, Stiles J. Functional MRI of global and local processing in children. Neuroimage 2002;16(2):415–424. [PubMed: 12030826]

Munakata Y, Yerys BE. All together now: when dissociations between knowledge and action disappear. Psychol Sci 2001;12(4):335–337. [PubMed: 11476102]

Nagy Z, Westerberg H, Klingberg T. Maturation of white matter is associated with the development of cognitive functions during childhood. J Cogn Neurosci 2004;16(7):1227–1233. [PubMed: 15453975]

O'Doherty J, Kringelbach ML, Rolls ET, Hornak J, Andrews C. Abstract reward and punishment representations in the human orbitofrontal cortex. Nat Neurosci 2001;4(1):95–102. [PubMed: 11135651]

O'Doherty JP. Reward representations and reward-related learning in the human brain: insights from neuroimaging. Curr Opin Neurobiol 2004;14(6):769–776. [PubMed: 15582382]

Pascual-Leone JA. A mathematical model for transition in Piaget's developmental stages. Acta Psychologica 1970;32:301–345.

Pecina S, Cagniard B, Berridge KC, Aldridge JW, Zhuang X. Hyperdopaminergic mutant mice have higher "wanting" but not "liking" for sweet rewards. J Neurosci 2003;23(28):9395–9402. [PubMed: 14561867]

Perez-Edgar K, Roberson-Nay R, Hardin MG, Poeth K, Guyer AE, Nelson EE, et al. Attention alters neural responses to evocative faces in behaviorally inhibited adolescents. Neuroimage 2007;35(4):1538–1546. [PubMed: 17376704]

Pine DS, Cohen P, Brook JS. Emotional reactivity and risk for psychopathology among adolescents. CNS Spectr 2001;6(1):27–35. [PubMed: 17008830]

Primus RJ, Kellogg CK. Pubertal-related changes influence the development of environment-related social interaction in the male rat. Dev Psychobiol 1989;22(6):633–643. [PubMed: 2792573]

Rauch SL, Shin LM, Wright CI. Neuroimaging studies of amygdala function in anxiety disorders. Ann N Y Acad Sci 2003;985:389–410. [PubMed: 12724173]

Reiss A, Abrams M, Singer H, Ross J, Denckla M. Brain development, gender and IQ in children. A volumetric imaging study. Brain 1996;119:1763–1774. [PubMed: 8931596]

Reyna V, Farley F. Risk and rationality in adolescent decision making: implications for theory, practice, and public policy. Psychological Science in the Public Interest 2006;7(1):1–44.

Rosenberg DR, Lewis DA. Changes in the dopaminergic innervation of monkey prefrontal cortex during late postnatal development: a tyrosine hydroxylase immunohistochemical study. Biol Psychiatry 1994;36(4):272–277. [PubMed: 7986893]

Rosenberg DR, Lewis DA. Postnatal maturation of the dopaminergic innervation of monkey prefrontal and motor cortices: a tyrosine hydroxylase immunohistochemical analysis. J Comp Neurol 1995;358(3):383–400. [PubMed: 7560293]

Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, et al. Functional frontalisation with age: mapping neurodevelopmental trajectories with fMRI. Neurosci Biobehav Rev 2000;24(1):13–19. [PubMed: 10654655]

Rubia K, Smith AB, Woolley J, Nosarti C, Heyman I, Taylor E, et al. Progressive increase of frontostriatal brain activation from childhood to adulthood during event-related tasks of cognitive control. Hum Brain Mapp 2006;27(12):973–993. [PubMed: 16683265]

Schlaggar BL, Brown TT, Lugar HM, Visscher KM, Miezin FM, Petersen SE. Functional neuroanatomical differences between adults and school-age children in the processing of single words. Science 2002;296(5572):1476–1479. [PubMed: 12029136]

Schultz W. Behavioral theories and the neurophysiology of reward. Annual Reviews of Psychology 2006;57:87–115.

ED_001854_00010733-00017

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Shin LM, Orr SP, Carson MA, Rauch SL, Macklin ML, Lasko NB, et al. Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. Arch Gen Psychiatry 2004;61(2):168–176. [PubMed: 14757593]

Silveri MM, Tzilos GK, Pimentel PJ, Yurgelun-Todd DA. Trajectories of adolescent emotional and cognitive development: effects of sex and risk for drug use. Ann N Y Acad Sci 2004;1021:363–370. [PubMed: 15251911]

Sobesky W. The effects of situational factors on moral judgements. Child Development 1983;54:575–584.

Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. Nat Neurosci 2003;6(3):309–315. [PubMed: 12548289]

Sowell ER, Thompson PM, Holmes CJ, Jernigan TL, Toga AW. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. Nat Neurosci 1999;2(10):859–861. [PubMed: 10491602]

Sowell ER, Thompson PM, Toga AW. Mapping changes in the human cortex throughout the span of life. Neuroscientist 2004;10(4):372–392. [PubMed: 15271264]

Spear LP. The adolescent brain and age-related behavioral manifestations. Neurosci Biobehav Rev 2000;24(4):417–463. [PubMed: 10817843]

Steinberg, L. Pubertal maturation and parent-adolescent distance: an evolutionary perspective. In: Adams, G.; Montemayor, R.; Gullotta, T., editors. Advances in Adolescent Behavior and Development. Newbury Park, CA: Sage Publications; 1989. p. 71-97.

Steinberg L. Risk taking in adolescence: what changes, and why? Ann N Y Acad Sci 2004;1021:51–58. [PubMed: 15251873]

Steinberg L. Cognitive and affective development in adolescence. Trends Cogn Sci 2005;9(2):69–74. [PubMed: 15668099]

Steinberg L, Cauffman E, Woolard J, Graham S, Banich M. Are adolescents less mature than adults? Minors' access to abortion, the juvenile death penalty, and the alleged APA "Flip-Flop". in press

Tamm L, Menon V, Reiss AL. Maturation of brain function associated with response inhibition. J Am Acad Child Adolesc Psychiatry 2002;41(10):1231–1238. [PubMed: 12364845]

Tarazi FI, Tomasini EC, Baldessarini RJ. Postnatal development of dopamine and serotonin transporters in rat caudate-putamen and nucleus accumbens septi. Neurosci Lett 1998;254(1):21–24. [PubMed: 9780082]

Teicher MH, Andersen SL, Hostetter JC Jr. Evidence for dopamine receptor pruning between adolescence and adulthood in striatum but not nucleus accumbens. Brain Res Dev Brain Res 1995;89(2):167–172.

Thomas KM, Drevets WC, Dahl RE, Ryan ND, Birmaher B, Eccard CH, et al. Amygdala response to fearful faces in anxious and depressed children. Arch Gen Psychiatry 2001a;58(11):1057–1063. [PubMed: 11695953]

Thomas KM, Drevets WC, Whalen PJ, Eccard CH, Dahl RE, Ryan ND, et al. Amygdala response to facial expressions in children and adults. Biol Psychiatry 2001b;49(4):309–316. [PubMed: 11239901]

Thomas KM, Hunt RH, Vizueta N, Sommer T, Durston S, Yang Y, et al. Evidence of developmental differences in implicit sequence learning: an FMRI study of children and adults. J Cogn Neurosci 2004;16(8):1339–1351. [PubMed: 15509382]

Turkeltaub PE, Gareau L, Flowers DL, Zeffiro TA, Eden GF. Development of neural mechanisms for reading. Nat Neurosci 2003;6(7):767–773. [PubMed: 12754516]

Volkow ND, Li TK. Drug addiction: the neurobiology of behaviour gone awry. Nat Rev Neurosci 2004;5(12):963–970. [PubMed: 15550951]

Yurgelun-Todd D. Emotional and cognitive changes during adolescence. Curr Opin Neurobiol 2007;17(2):251–257. [PubMed: 17383865]

Yurgelun-Todd DA, Killgore WD. Fear-related activity in the prefrontal cortex increases with age during adolescence: a preliminary fMRI study. Neurosci Lett 2006;406(3):194–199. [PubMed: 16942837]

Zald DH, Boileau I, El-Dearedy W, Gunn R, McGlone F, Dichter GS, et al. Dopamine transmission in the human striatum during monetary reward tasks. J Neurosci 2004;24(17):4105–4112. [PubMed: 15115805]

ED_001854_00010733-00018

Zehr JL, Todd BJ, Schulz KM, McCarthy MM, Sisk CL. Dendritic pruning of the medial amygdala during pubertal development of the male Syrian hamster. J Neurobiol 2006;66(6):578–590. [PubMed: 16555234]

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

ED_001854_00010733-00019

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

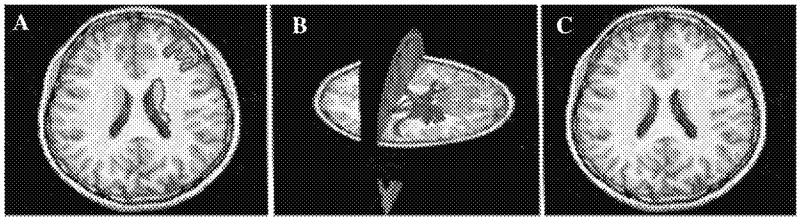


FIGURE 1.
Illustrations of the most common magnetic resonance methods used in the study of human development. **(A)** Structural magnetic resonance imaging (MRI) to produce structural images of the brain useful for anatomical and morphometric studies, **(B)** diffusion tensor imaging (DTI) measures myelination and directionality of fiber tracts between anatomical structures, and **(C)** functional MRI (fMRI) measures patterns of brain activity within those structures (from Casey et al. 2005).

ED_001854_00010733-00020

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

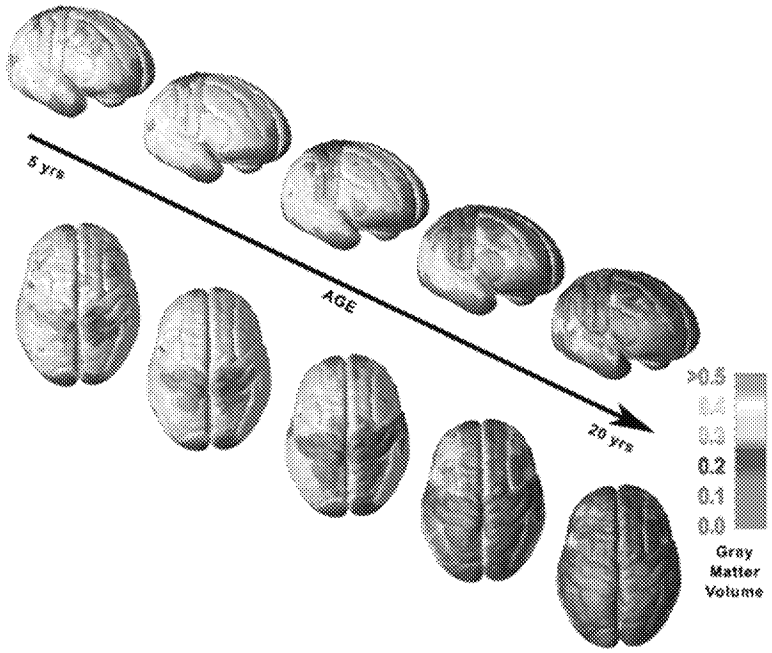


FIGURE 2.
Illustration of gray matter volume maturation over the cortical surface from 5 to 20 years of age (from Lenroot & Giedd 2006).

ED_001854_00010733-00021

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

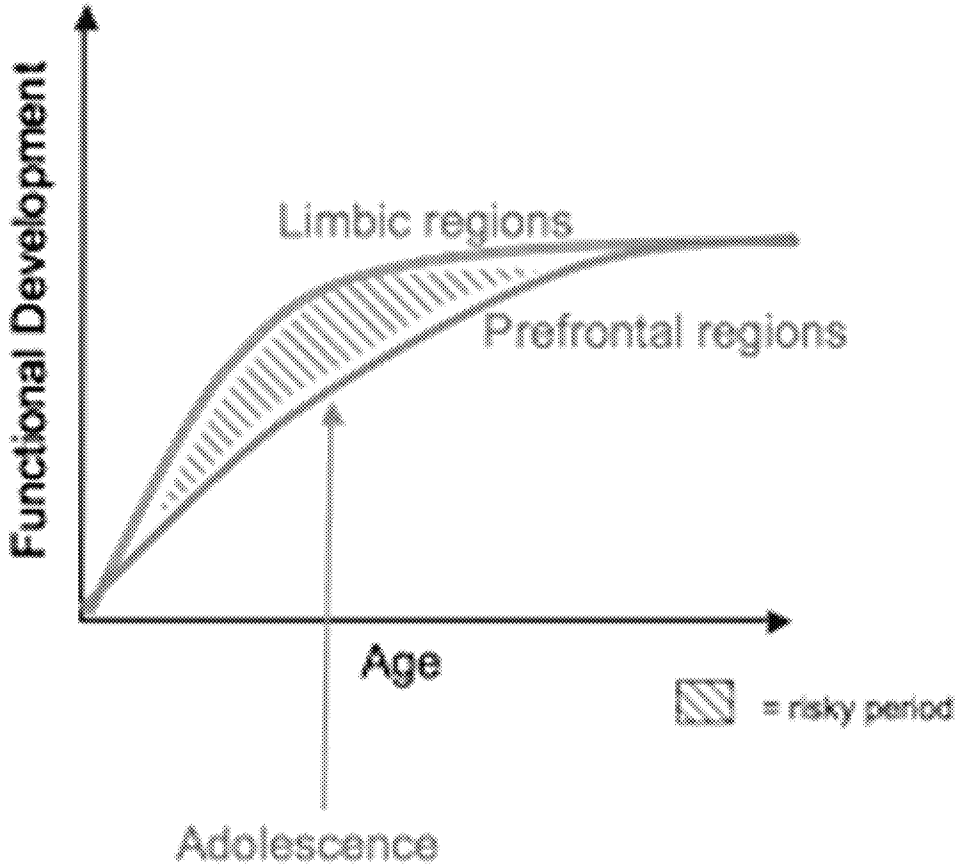


FIGURE 3.
The traditional explanation of adolescent behavior has been that it is due to the protracted development of the prefrontal cortex. Our model takes into consideration the development of the prefrontal cortex together with subcortical limbic regions (e.g., nucleus accumbens and amygdala) that have been implicated in risky choices and emotional reactivity.

ED_001854_00010733-00022

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

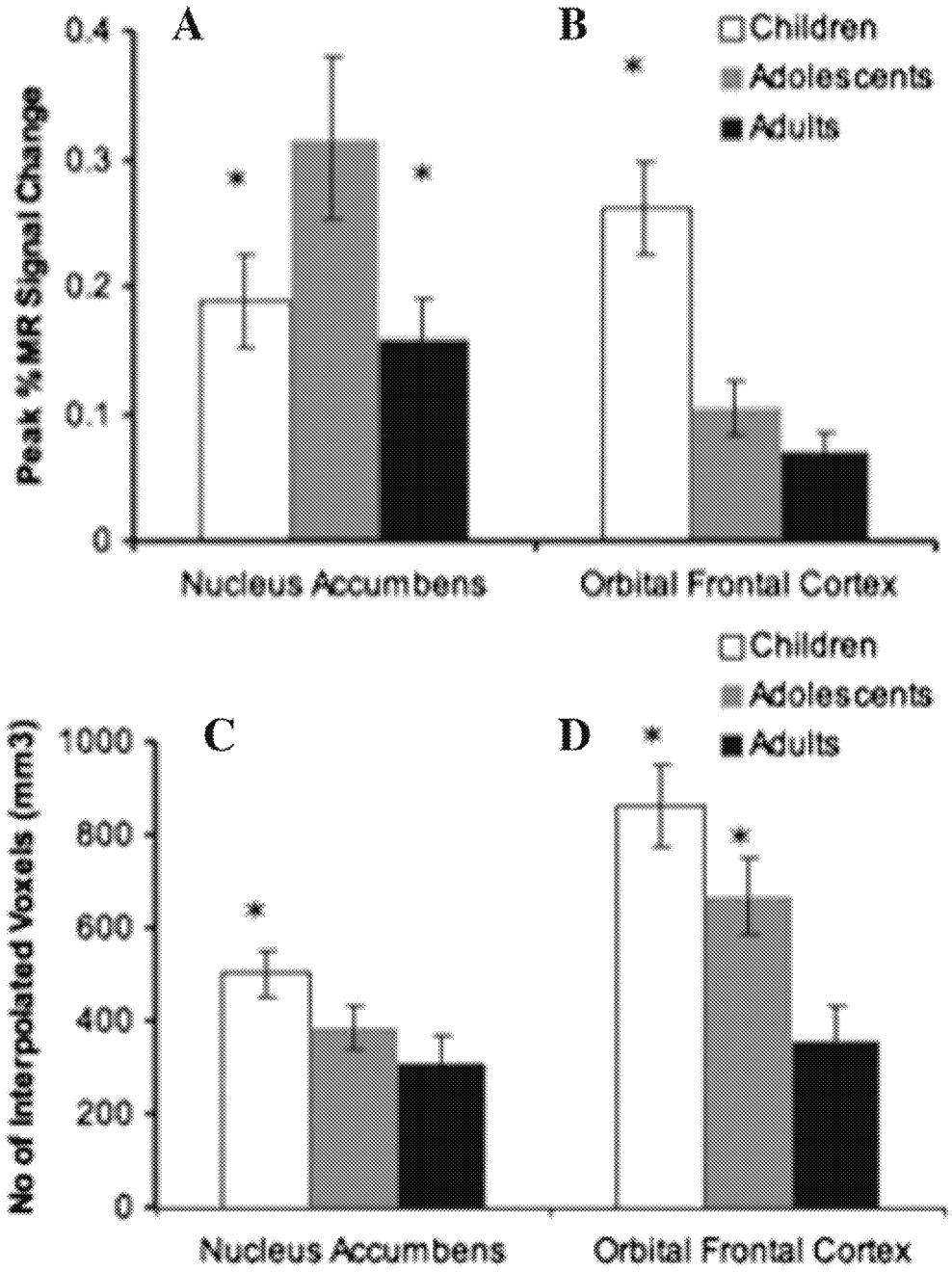


FIGURE 4.

Magnitude and extent of accumbens and OFC activity to reward. Adolescents (13–17 years) showed greater percent signal change to large rewards than either children (aged 7–11 years) or adults (23–29 years) in the accumbens **(A)**. Children had the greatest percent signal change in the OFC compared to adolescents and adults **(B)**. Children had the greatest volume of activity in the accumbens relative to adolescents and adults **(C)** Children and adolescents showed greater volume of activity in the OFC than adults **(D)**. Adapted from Galvan et al. (2006).

ED_001854_00010733-00023

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

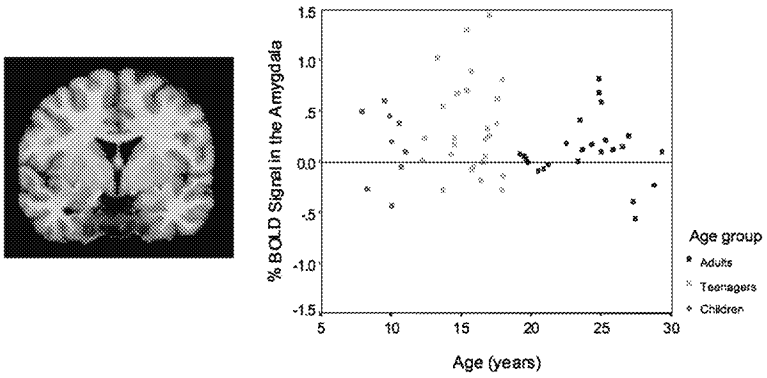


FIGURE 5.
Bilateral amygdala activation (left). Graph depicts amygdala activity in adults, teenagers, and children. Adapted from Hare et al. (in press).

ED_001854_00010733-00024

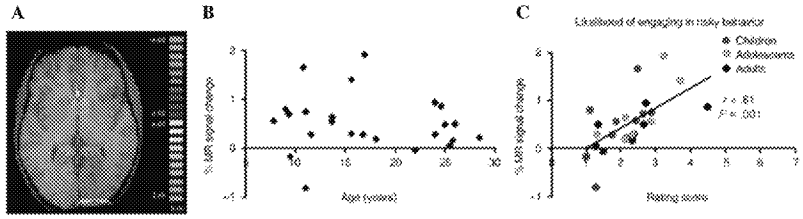


FIGURE 6.
Activity in the nucleus accumbens in anticipation of reward **(A)**. Percent change in fMRI signal in the accumbens in anticipation of reward as a function of age **(B)**. The association between accumbens activity to reward and the likelihood of engaging in risky behavior in three age groups **(C)** (Adapted from Galvan et al. 2007).

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

ED_001854_00010733-00025

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

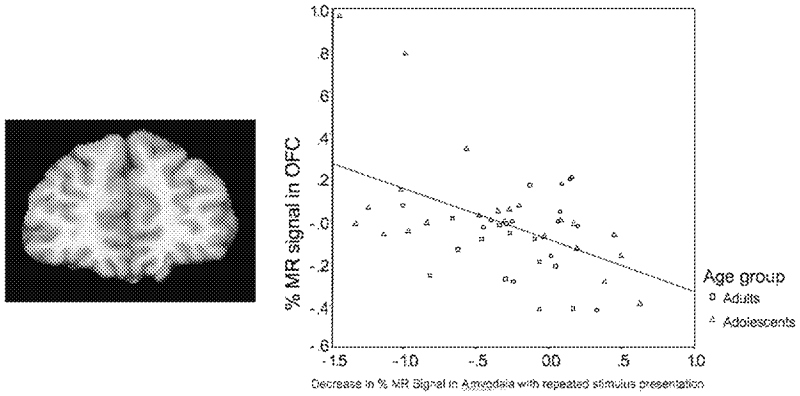


FIGURE 7.
Picture depicts left orbitofrontal activity. Graph illustrates correlation of activity in the OFC and in the amygdala in both adults and adolescents (adapted from Hare et al. in press).

ED_001854_00010733-00026

Journal of Physiology - Paris 104 (2010) 279–286

Contents lists available at ScienceDirect

Journal of Physiology - Paris

journal homepage: www.elsevier.com/locate/jphysparis

Adolescent brain development, risk-taking and vulnerability to addiction

Jacques Dayan [a,b,*], Alix Bernard [c], Bertrand Olliac [d], Anne-Sophie Mailhes [b], Solenn Kermarrec [b]

[a] Inserm-EPHE-Université de Caen/Basse-Normandie, Unité U923, GIP Cyceron, CHU Côte de Nacre, Caen, France
[b] Service Hospitalo-Universitaire de Psychiatrie de l'enfant et de l'adolescent, Université de Rennes 1 et CHGR, France
[c] Equipe d'accueil 2646, PPI, Université d'Angers, France
[d] Service Hospitalo-Universitaire de Psychiatrie de l'enfant et de l'adolescent, Université de Limoges, France

ARTICLE INFO

Keywords:
Adolescent
Risk
Addiction
Prefrontal cortex
Psychoanalysis
Neuroimagery

ABSTRACT

Adolescents (12–18 years old) and young adults (18–25 years old), are more likely than older adults to drive-or agree to be driven-recklessly or while intoxicated, to use illicit or dangerous substances and to engage in both minor and more serious antisocial behaviour. Numerous factors during adolescence may lead to or favour initiation of drug use, such as sensation-seeking, gregariousness and social conformity. These aspects, however, cannot be dissociated from the increased sex drive and quest for an integrated self. In the separation-individuation process, relationships with peers play many different roles: a field for experimentation, emotional support, a place for "projection" and "identification", and the possibility of finding a partner. Unsurprisingly, therefore, drug use generally takes place in a group setting. Despite evidence of heightened real-world risk-taking, laboratory studies have yet to yield consistent evidence that adolescents, when on their own, are more inclined towards risky behaviour than their elders. Moreover, their comprehension and reasoning abilities in risky decision-making situations are roughly equivalent to those of adults. Structural and functional neuroimaging studies have shown that neural circuitry undergoes major reorganization during adolescence, particularly in those regions of the brain relating to executive functions, the self and social cognition, and that the "emotional brain" may play a role in that reorganization. Age-related decreases in gray matter volume mainly reflect a reduction in the number of synapses and the complexity of axonal ramifications. By 18–20 years old, most of the subcortical white matter and association pathways have reached a plateau. Risk-taking behavior and novelty-seeking may provide, with an appropriate feed back, a mechanism to optimize brain development in adolescence.

© 2010 Elsevier Ltd. All rights reserved.

1. Introduction

Cross sectional and, more recently, longitudinal studies have demonstrated that the prevalence of drug use increases noticeably during adolescence, peaking in late adolescence and early adulthood (Degenhardt et al., 2008; Johnston et al., 2007). For instance, in a representative sample of 8098 subjects aged 5–54 years (US National Comorbidity Survey), Wagner and Anthony (2002) estimated peak values for initiating alcohol and marijuana use at 18 years and cocaine use at 20 years, using survival analysis techniques. Individuals drink their heaviest in their late teens and early to mid-twenties, with 44% of college students displaying binge drinking every 2 weeks (Wechsler and Kuo, 2000). The natural history of tobacco smoking in adolescence is variable, with phases of cessation, reduced use and relapse. In a longitudinal study, Van De Ven et al. (2010) found that the prevalence of nicotine dependence in young adults was 16.9% for adolescent smokers. Substance experimentation during adolescence elevates the risk of persistent substance use and substance use disorders in later life stages for all types of drugs (Palmer et al., 2009; Bauman and Phongsavan, 1999; Brook et al., 1999; Kapusta et al., 2007; Riggs et al., 2007; Winters et al., 2008). Given that increased risk-taking during adolescence (Furby and Beyth-Marom, 1992) has consistently been regarded as a major risk factor for initiating drug use during this period, we discuss how cognitive neuroscience, particularly data provided by neuroimaging studies, can complement psychoanalytic constructs and thus enhance our understanding of this subject.

2. Risk-taking during adolescence: a psychoanalytic perspective

Psychoanalytic theories of adolescence consider exploratory behaviour to be a normal, and even necessary (philosophically speaking), component of development during this period. Exploration is motivated by several concomitant factors, such as the search for a sexual partner, at a time of redefinition of the self and the quest for self-affirmation. This is set against the backdrop of a weakened sense of security, as adolescents drift away from their parents and

* Corresponding author. Address: Laboratoire Unité U923, CHU Côte de Nacre, Caen, France. Tel.: +33 011 336 62 57 89 04.
E-mail address: dayan-j@chu-caen.fr (J. Dayan).

0928-4257/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jphysparis.2010.08.007

ED_001854_00010734-00001

start to entertain ambivalent feelings towards them. In this complex and uncomfortable context, adolescents are prone to seek an immediate solution to their internal or external conflicts and, accordingly, to favour immediate action. Although there are considerable interindividual variations in behaviour, this tendency may result in an increase in psychosocial and physical damage. For many adolescents, action serves as a major testing ground for the process of self-definition (Blos, 1967, 1980, 1989; Erikson, 1956). Adolescence is the first time that an individual's sexual identity and sense of him- or herself as a sexual being is principally measured by what he or she does, rather than simply wishes to do, and not just by what his or her parents say or how they react (Ritvo, 1971). However, this is true not only for sexual identity and behaviour, but also for a wide range of other behaviours which help to shape social identity. Both the quality of their emotional experiences (valence and intensity) and the judgments of their peers contribute to the fine-tuning of adolescents' actions and values. This process of self-definition through action ultimately makes an important contribution to the relatively stable self-representations of adulthood.

The first psychoanalytic conceptualization of adolescence (Freud, 1905) focused on the revival and transformation of infantile development and infantile conflict, both preoedipal and oedipal, by the biological event of sexual maturation. Freud regarded adolescence as a transitional period, during which new solutions to infantile internal conflicts become possible due to psychic and sexual maturation. This theory, however, had limited efficacy in the treatment of adolescent disorders. New theories subsequently emerged, mainly after the Second World War, in which narcissistic preoccupations and the construction of the self became central. In a sense, self was seen as a psychosocial processing system as it was to be in later neurocognitive constructs (Klaczynski, 2004). However, previous key concepts, such as the importance of sex drive (libido) and (unconscious) conflict theory, were retained in the psychoanalytic model. There were many similarities between the observations and key theoretical points made by the most eminent researchers of the day, such as Blos and Erikson in the United States and Winnicott in Europe. Although the impact of sexual maturation on behaviour, mood, thought and affect was confirmed by treatment, other key concepts were actively investigated, in order to improve the efficiency of the therapy. Thus, the search for a coherent identity, an integrated self, in a period of metamorphosis, correlative to new desires and new abilities, emerged as a central construct. Erikson (1956) described what he called the adolescent task of "weaving internal tastes, talents, and values together with elements of one's life history and the demands of one's culture into a coherent identity". From a developmental perspective, adolescence can be understood as "passing stages of tentative role tryouts of the new pubertal self in all its potential realizations working synergically toward a postchildhood identity" (Blos, 1962). According to Blos, this process brings in its wake a decrease in developmental plasticity, metaphorically speaking, and a growing rigidity of the personality. New findings on brain development tend to confirm this observation. This final phase of reduced plasticity corresponds to the emergence of character.

Blos (1958, 1989) emphasized another crucial point in the development of adolescents, namely the need for social recognition of their ability to function as an autonomous and personal self, in the form of "a confirmation of their gender, as manifested in social expressions, realized in fantasy, self-gratification, or bodily affective interaction with the same or other sex". Self-idealization is also a typical aspect of adolescence and serves to regulate self-esteem (Blos, 1958, 1967). This period is usually characterized by changing behaviours, accompanied by mood swings, increased withdrawal, a disposition towards social isolation, but at the same time insatiable and irrepressible gregariousness. Relationships oscillate between being active and passive and between sharing with others, including peers and parents, and being shared by them. Winnicott (1965) emphasised the challenge faced by adolescents when they acquire the physical abilities "for genital experience and also for actual killing" that were only fantasies in their childhood. He referred to the necessity, in terms of the development of the personality structure (ego), of "experiencing instinctual drives and the object relationships that have the instinctual drives as a basis". Hence, this "experiencing", which inevitably leads to an increased rate of risky behaviour, is regarded as a component of any "healthy" adolescence.

High-risk behaviours may also be displayed by adolescents suffering from mental disorders, such as antisocial personality or affective disorders. As the causes of these types of behaviours are, to a certain extent, the same for all adolescents, they can shed light on the risky behaviours of healthy individuals. Narcissistic rage and violent behaviours, or withdrawal of cathexis, may emerge in response to disillusionment with parents, common to both healthy and vulnerable adolescents. In view of this, adolescence may be best understood through the prism of the developmental phase of early childhood.

For adolescents, an excess of activity is no more "risky" than an excess of passivity. During adolescence, the psychic conflict between the activity and passivity of the ego is reflected in an externalized conflict over action: the ego's task is to restrain and contain impulses, as well as to release and gratify them. It should be noted here that the term "ego" is sometimes used in the literature to replace "self" and refers to a construct that is indeed vaguely similar to self and not so very far removed from the cognitive concept of "central executive" (Bornstein, 2005). Similarly, there are a number of discrepancies between the terms used to characterise adolescent behaviours. For example, it is commonly said that "adolescents are characterised as impulsive" and prone to "risk-taking", with these constructs sometimes being used synonymously. However, although adolescents may be impulsive in some situations, they may also be passive and inhibited, while adults routinely react promptly and even impulsively. Rates of accidental deaths or injuries in the United States and Europe, for instance, are higher among young adults (18–25 years) than among adolescents. Peaks for drug use and dependence, although they vary according to the country being studied, often occur around or after 18 years.

When adolescents find themselves in a situation with no acceptable solution for the preservation of their self-esteem or self-identity, they may choose a risky solution. This relatively frequent attitude may be described as impulsive, but also underlines the adolescent's need to preserve his or her future, as ethical choices predominate at this stage of development. Another behaviour which may be called impulsive is "acting out", an unconscious ego defence mechanism which is brought into play when individuals engage in some kind of behaviour that serves to ease the emotional pain and anxiety associated with an unconscious conflict between their drive and their conscience.

2.1. Risk-taking alone is not a sufficient condition for addiction

Freud (1927) wrote that human beings cannot avoid using "sedatives", of which there are at least three kinds: those that decrease our suffering, those that give us substitute satisfactions and those that make us insensitive to our misery. According to this statement, every civilization uses drugs and a large number of human beings experience drugs during adulthood. In some cases, drug use is associated with mental disorders, such as antisocial behaviour disorder, posttraumatic stress disorder, depression and narcissistic personality disorder. Addiction differs from simple use or even misuse because it is a compulsive, self-maintained phenomenon. Drug use, particularly if repeated, allows individuals to ascribe less importance to relationships and decreases torments and wor-

ries about their social life. According to Freud, in a letter to Fliess dated 22 December 1897, (Freud, 1985) the prototype of addiction ("the great habit") is masturbation, a narcissistic and mechanically driven source of satisfaction, associated with a repetitive and impoverished fantasy life, and "alcohol, morphine, tobacco are only substitutes". When drugs gradually invade people's lives, representations associated with the use of the toxic substance increasingly take the form of "memories in the body" (Gaddini, 1992) or "symbolic equations" (Segal, 1957), and generally obey the rules of the primary process (Freud, 1900). Freud (1912) also propounded the notion of competition between normal sexuality and the compulsion for a particular substance in the case of addiction. He later wrote that intoxication is a means of escape from pain, substituting the pleasure principle for the reality principle (Freud, 1927) According to Glover (1932b), drugs appear to obliterate instinctual tension or frustration, by "cutting off" the outside world. This accounts for the extreme sense of compulsion associated with addiction. However, as the latter is a process associated with a specific brain dysfunction that seems to be similar for adolescents and adults, it will not be studied here.

2.2. The path to addiction can be understood as resulting from an inability to tolerate affect

Although drug use is frequently initiated during adolescence, it has yet to be established whether single or even repeated use is enough for an individual to become addicted. As previously reported, the peak for drug initiation is after 17 years, depending on the substance (with the exception of tobacco), and the peak for dependence after 18 years. It could therefore be argued that addiction is primarily a phenomenon of early adulthood.

Drugs relieve psychological suffering. According to Khantzian (1997) opiates attenuate feelings of rage or violence, alcohol relieves feelings of isolation, emptiness and anxiety, and stimulants can increase hypomania, relieve depression and counteract hyperactivity and attention deficit. Although prolonged self-medication may lead to addiction, it does not appear to be the main cause. Addiction, which presupposes craving and dependence, has been linked to early developmental failures (Johnson, 1999) leading to an inability to tolerate affects and thence to regulate self-esteem or relationships (Krystal, 1982; Zinberg, 1975). To conclude, the psychoanalytical approach distinguishes between simple drug use and addiction, although their causation and maintenance may overlap. In adolescence, the former results mainly from the tendency to explore the environment with one's peers, although a reduction in one's active fantasy life and high levels of anxiety are often involved in addiction. Unsurprisingly, therefore, drug use generally takes place in a group setting and involves a degree of social ritualism-two elements which play a major role in combating anxiety and distress (Glover, 1932a; Johnson, 1999; Johnson et al., 2000; Khantzian, 1997; Hopper, 1981). Moreover, in the case of addiction, uncertainty in social, sexual and affective relationships tends to disappear, to be replaced by highly conventional and ritualized behaviours, leading to compulsory satisfaction. Hence, faced with the pressure of a burgeoning sex drive and the need to engage in relationships, vulnerable personalities unable to withstand deceit, distress, shame, anger and anxiety may find in addiction a substitute for real life. Self-coherence is, at least for a while, maintained with the support of the drug.

3. Risk-taking during adolescence: neuropsychological aspects

The advent of neuroimaging has profoundly modified our knowledge of adolescent brain development acquired from animal or post mortem studies.

Structural and functional neuroimaging studies have revealed that neural circuitry undergoes a major reorganization in adolescence, particularly in those regions of the brain involved in executive functions, the self and social cognition. Functional neuroimaging has shown that these regions also play a key role in the regulation of behaviour and emotion, and in the perception and evaluation of risk and reward. Accordingly, "impulsivity, risk-taking behavior, and novelty-seeking may provide a mechanism to expand the range of possibilities that will then provide the appropriate feedback for optimal sculpting of the brain" (Luna et al., 2001).

3.1. Structural neuroimaging

Most studies of structural brain development take the form of either magnetic resonance imaging (MRI) measurements of grey matter (GM) and white matter (WM) volumes or, more recently, diffusion tensor imaging (DTI) investigations of the macro- and microstructure of WM. Results are consistent, whether they are yielded by cross-sectional studies, some with large cohorts of children ($N > 200$), or by the somewhat sparser longitudinal studies, generally involving smaller samples (Gogtay et al., 2004; $N = 13$) though with some notable exceptions (Shaw et al., 2006; $N = 307$).

3.1.1. Grey matter maturation

Put succinctly, GM volume undergoes a prepubertal increase, followed by a postpubertal loss. Considerable developmental changes occur in GM volume, density and cortical thickness between childhood and adulthood. Age-related decreases in apparent GM volume mainly reflect a reduction in the number of synapses and the complexity of axonal ramifications, due to accelerated elimination or "synaptic pruning", with an attendant increase in the degree of myelination of intracortical axons. Cortical complexity decreases during adolescence in both the left and right hemispheres (White et al., 2010). Overall, GM volumes display heterogeneous developmental trajectories across the major lobes, peaking in the frontal lobes at around 11 years, but continuing to increase in the temporal lobes until 14 years. Longitudinal studies of GM development at functionally *subregional* levels also point to heterochronic maturational trajectories. Typically, the primary sensorimotor cortices and the frontal and occipital poles mature first, with maturation proceeding rostrally, from the parietal areas to the frontal ones, and caudally and laterally over the parietal, occipital and, late after adolescence, temporal cortices.

The dorsolateral prefrontal cortex (DLPFC) and the superior temporal cortex, which contain association areas that integrate high-level information in several sensory modalities, are the last to mature, after 16–17 years (Gogtay et al., 2004), suggesting that the higher-order association areas only mature after the lower-order sensorimotor regions, whose functions they integrate, have matured. The DLPFC serves as the highest-order cortical area, responsible for executive functions such as motor planning, organization and regulation. It is also involved in working memory. The superior temporal gyrus (STG) has also been identified as a critical structure in social cognition. The reduction in size of the DLPFC at the end of adolescence suggests that pruning/myelination may occur in parallel (Giorgio et al., 2010; Gogtay et al., 2004). Three recent studies examined changes in regional cortical thickness in relation to various cognitive functions, namely IQ for Shaw et al. (2006), memory for Sowell et al. (2001a,b) and executive functions (inhibition, shifting and updating) for Tamnes et al. (2010). Children with the best scores demonstrated a particularly plastic cortex, with an initial accelerated and prolonged phase of cortical increase followed by a particularly vigorous phase of cortical thinning. Frontal lobe GM thinning was also more strongly predictive of memory capacity (Sowell et al., 2001a,b). GM reduction in the

frontal cortex observed between adolescence (12–16 years) and early adulthood (23–30 years) is also associated with changes in the striatum, putamen and globus pallidus-structures implicated in risk-taking. The maturation of these frontostriatal regions may be subserved by enhancing long-distance connectivity in different WM tracts, and then increasing the "fine-tuning" of neuronal connectivity. In adults, complex tasks may be accomplished more automatically, with the recruitment of phylogenetically ancient parts of the brain such as the striatum and cerebellum.

3.1.2. White matter maturation

Contrary to GM, WM volumes increase roughly linearly throughout the first four decades of life, with a peak around the mid-forties, when speed for certain fine motor skills is also optimal. Lebel et al. (2008)'s extremely interesting study conducted on a large sample ($N = 202$, aged 5–30 years) showed that the brain undergoes major microstructural changes during adolescence and indeed beyond, until 25 years. By 18–20 years, most of the subcortical WM and association pathways have reached a plateau. However, significant maturation has been observed between 20 and 25 years, notably of the corticospinal tract, lenticular and caudate nuclei, and thalamus. The cingulum and the uncinate fasciculus continue their maturation beyond 25 years. This study is one of several reporting nonlinear development, with frontal tracts maturing later than the more posterior ones (Lenroot et al., 2007). The exponential development of WM during adolescence may be regarded as a continuation of the exponential patterns of development observed during infancy and early childhood (during the first 5 years of life, fractional anisotropy (FA) values increase by up to 200%).

Some studies have associated DTI indices with cognitive measures, such as intellectual abilities (Schmithorst et al., 2005) and, more recently, verbal skills. In a group of 168 participants aged 8–30 years, Tamnes et al. (2010) found that *high verbal* abilities were associated with accelerated WM development in late adolescence/early adulthood before reaching a plateau, unlike *average verbal* abilities, which were correlated with more protracted development that continued into early adulthood. Liston et al. (2006) reported a relationship between frontostriatal radial diffusivities and inhibition abilities. Once more, these studies highlight the importance of the frontostriatal network in the development of executive functions.

A handful of studies have combined volume- and tract-based analyses. In 2010, Giorgio et al. reported the first longitudinal study to have focused on the adolescent period (13–18 years). Data showed that GM volumes decreased in many cortical areas, including higher-order association areas, such as the DLPFC, as well as in primary sensorimotor and sensory cortices. Conversely, WM volumes increased in several regions, notably the frontal lobe, corpus callosum and arcuate fasciculus.

In conclusion, neuroimaging studies have shown that an extensive reorganization of neural circuitry takes place during adolescence, particularly in those regions of the brain involved in executive functions, the self and social cognition. This reorganization primarily constitutes a simplification of neural circuitry and could be interpreted as the optimisation of the neural circuits involved in high-level tasks. Although the conditions governing synaptic pruning have yet to be fully elucidated, these modifications probably have an adaptive value and are determined, at least in part, by the experiences of pleasure or displeasure resulting from the various strategies used by adolescents in the new and complex tasks that they are called upon to undertake during this period. The development of WM fibres allowing faster or more intense connections between different areas of the brain could well contribute to these changes. Then again, as it is a secondary phenomenon and takes place over a protracted period, it may simply serve to establish connections between brain regions that have already undergone considerable maturation. It has been suggested that the gyrification that occurs between childhood and adolescence, as opposed to the gyrification that is observed in the first months of life and which is mainly mediated by genetics, may be influenced mainly by the environment and thus by the individual's own experiences. Studies of twins have confirmed the validity of this approach. Gyrification in adolescence (White et al., 2010) may well be triggered by the development of white matter fibre tracts connecting more or less widely separated areas of the brain. An individual's specific experiences may influence the way in which these tracts are organized.

3.1.3. Sexual dimorphism

Recent MRI studies have reported sexual dimorphism in the development of brain structure and function during adolescence (Lenroot and Giedd, 2010; Schmithorst et al., 2008). First, total brain volume is about 10% greater in males, and peaks at 10.5 years in females and 14.5 in males (Lenroot et al., 2007). The GM trajectory also peaks 1–2 years earlier in females, while males may have a steeper rate of WM development during adolescence. Studies using magnetization transfer ratio (MTR) values also point to a possible sexual dimorphism during adolescence, involving an increase in axonal calibre in males (Perrin et al., 2008), as opposed to increased myelination in females (Perrin et al., 2009). Sexual dimorphism can also be observed at a regional level. The regions most frequently reported by imaging studies as displaying morphological sex differences include the basal ganglia (larger in females) and limbic structures (larger hippocampus and smaller amygdala in females). Concerning WM, a study of a large group of children and adolescents found greater FA in boys, in associative WM regions (including the frontal lobes), and greater FA in girls, in the splenium of the corpus callosum (Schmithorst et al., 2008). Increasing FA values reflect increasing myelination or increases in axonal calibre and possibly increasing fibre organization, resulting in decreased tortuosity. This variability has notable behavioural consequences. For instance, a study in 21 adolescents, looking at impulse control, found that different WM regions were associated with task performance in male and female adolescents (Silveri et al., 2006).

3.2. Functional neuroimaging: exploration and risk-taking

Neuroimaging studies can often complement or extend purely behavioural studies, which have yielded the following main findings.

3.2.1. Behavioural studies

In cognitive psychology, risk-taking has been associated with an increased tendency towards sensation-seeking and immediate reward-seeking, and a lack of inhibition (Tamm et al., 2002). Some authors, focusing on cognitive abilities, have suggested that adolescents are less *liable* to *consider* the negative repercussions of rewarded behaviour in hypothetical scenarios (Reppucci, 1999). However, this opinion is controversial and there is substantial evidence that adolescents are well aware of the risks they take, with few differences found between adolescents and adults in the spontaneous mention of the costs and benefits associated with several risky actions (Alexander et al., 1990; Beyth-Marom et al., 1993). Moreover, there is little evidence of any systematic improvement in logical abilities related to decision-making past 16 years (Overton, 1990). Increasing adolescents' awareness of various risks has little impact on their decision-making outside the laboratory. Differences between adolescents and adults may rely more on the inability of the former to automatically engage in social rules. Cauffman and Steinberg (2000) examining how a sample of over a

thousand participants aged 12–48 years scored on "socially responsible decision-making" found that, on average, adolescents aged below 18–19 years scored significantly lower than adults. However, there were considerable interindividual differences in judgments within each adolescent age group.

These data can be more easily understood if we consider the process of socialization among adolescents, as relations with peers play a major role in the construction of the "social self". Typical laboratory studies of risky decision-making fail to consider the social context in which risk-taking occurs in "real life" (Steinberg and Cauffman, 1996; Steinberg, 2004, 2008, 2010). In such studies, individual adolescents are presented with hypothetical dilemmas under conditions of low emotional arousal and are then asked to make and explain their decisions. In the real-world, adolescents often make decisions under conditions of emotional arousal and in peer groups. Heightened levels of susceptibility to peer influence have been shown to characterize adolescence even in laboratory studies (Steinberg and Silverberg, 1986). Gardner and Steinberg (2005) showed that the participation of peers (two friends) in a driving simulation video game led to an increase in risky driving for adolescents, but not for adults. Adolescents showed the same level of risk-taking as adults when they were alone. This has prompted some to argue that age differences in risky behaviour may be better accounted for by differences in psychosocial functioning than by differences in more cognitive aspects of risk orientation, such as risk preference (Steinberg and Cauffman, 1996).

Adolescents tend to base decisions on temporally proximal outcomes rather than on distal ones (Gardner and Herman, 1991), and in some contexts, are better motivated by reward than by negative reinforcement (Arnett, 1992; Gardner and Herman, 1991). In a psychodynamic construct, these trends reflect the complex quests undertaken by adolescents and their need to experience and socialize, at a time when the values of the past are being deeply questioned and yet the values of the future remain uncertain, and when adolescents need their actions to be validated by their peers. To put it more dramatically, actions focusing on immediate reward may also be explained by "uncertainty about the meaning and the value of life" (Winnicott, 1965).

3.2.2. Exploration and risk-taking as seen through functional neuroimaging

Structural studies have highlighted significant changes in many regions of the prefrontal cortex, notably the dorsolateral and ventromedial regions, throughout adolescence. These changes help to improve various executive functions which contribute to the regulation of affect and behaviour. The dorsolateral part of the prefrontal cortex is preferentially involved in executive processes and working memory, while the ventromedial part is involved in emotional regulation (Stuss and Alexander, 2007). For their part, functional studies point to a particularly highly developed functional link between these highly evolved structures and the limbic system during adolescence.

Studies featuring inhibition tasks can increase our understanding of impulsive behaviours. Inhibition may generally be defined as a function which, when the organism is faced with many possible responses, favours one particular response without simultaneously activating the others. Many behavioural studies have focused on cognitive control, or inhibition, using flanker, Stroop or go/no-go tasks. These tasks assess different kinds of inhibition but which all share a common mechanism, namely the inhibition of a proponent or automatic response. On the whole, children and adolescents activate a larger cerebral network to perform the tasks than adults. Thereafter, the number of brain regions that are recruited decreases with age, so that only essential regions associated with the task are activated (Durston et al., 2002; Luna et al., 2001; see Casey et al., 2008, for review). When Luna et al. (2001) compared three age groups, they found that adolescents displayed a greater volume of activation in the DLPFC during a response inhibition task than either younger children or older adults, suggesting a greater reliance on the frontal executive network. A recent meta-analysis of the development of executive functions using functional MRI (fMRI) highlighted the role of the dorsolateral and inferior prefrontal cortices-regions which undergo major reorganization during adolescence. We can hypothesise that synaptic pruning and relative disconnection enable regions such as the DLPFC to do the computations needed for the most efficient executive functioning, while an increase in myelination, continuing into adulthood, allows regions far from the DLPFC, such as the lateral cerebellum (Luna et al., 2001), to join in and assist in more consistent and automatic control of behaviour.

Other regions deserve further consideration. For instance, the involvement of the right anterior insular cortex is specific to adolescents as is not seen in either children or adults. This is remarkable, considering the involvement of this particular region in addiction (Naqvi and Bechara, 2009), self-regulation and executive functions.

3.2.2.1. The role of the limbic cortex in the control of risky behaviours. Hare et al. (2008) found that adolescents displayed exaggerated amygdala activity relative to children and adults during an emotional go/no-go task. They suggest that this greater activity may reflect the need to compensate for relatively weak anatomical connections between the brain regions involved in the task, through greater "top-down" executive control (Stevens et al., 2007). Conversely, the ventrolateral prefrontal cortex (VLPF) has been shown to modulate amygdala engagement in both adolescents and adults, in order to facilitate flexible attention and behaviour when responding to environmental threats (Monk et al., 2003, 2008). The greater activity observed in the VLPFC, a region massively interconnected with the amygdala, during a go/no-go task suggests that both regions are strongly involved in this form of executive control (Stevens et al., 2007).

Wood et al. (2005) have shown that the left VLPFC mediates *positive* representations (of a concept or object) and their emotional assessment, whereas the right DLPFC mediates *negative* representations and the amygdala evaluative processing.

Casey et al. (2008) have postulated that high risk-taking during adolescence is due to discrepant development between limbic and prefrontal top-down control regions. They base their conclusions on animal studies (Laviola et al., 1999) and imaging studies (Spear, 2000, 2002; Ernst et al., 2005; Galvan et al., 2006, 2007). According to this model, adolescent behaviour is governed mainly by limbic regions, as they are functionally more mature (i.e., imbalance of limbic relative to prefrontal control), whereas in children the limbic and prefrontal regions are both still developing and in adults, these systems are fully mature. According to the authors, in emotionally salient situations, the limbic system will win over control systems in adolescents.

Although no firm conclusion can yet be drawn from these studies, it is probable that the limbic system play a major role of regulation during adolescence. However, this role looks complex. Given the need for exploratory behaviours and risk-taking, the mature limbic system may well play a positive role, regulating and moderating an immature frontal system.

3.2.2.2. The reward system: discrepant hypotheses about the role of the ventral striatum in risk-taking. In the experimental exploration of reward processing, different emotional and cognitive processes can be described. Some authors differentiate between risk-seeking (general approach to rewards) and risk-taking (positive engagement in the context of uncertainty). Other authors make a distinction between anticipation and consummation. For instance,

anticipating the opportunity to respond for monetary gain activates regions of the ventral striatum (VS), an archaic region of the brain, whereas notification of successful responses recruits a region of the medial frontal cortex (MFC), a region dedicated to complex tasks (Knutson et al., 2001a,b). The VS responds more automatically to appetitive cues (Knutson et al., 2001a), whereas the MFC appears to direct its energy towards appropriate goal objects (Elliott et al., 2000). Some studies (Spear, 2000) posit that the striatum is relatively hyporesponsive to rewards during adolescence, such that heightened reward-seeking behaviour is needed to achieve the same activation as in adults. An alternative and preferential hypothesis suggests that during adolescence, the striatal reward system is hyperresponsive, resulting in greater reward-seeking. Disproportionately increased activation of the VS motivational circuit may result from the influence of defective or immature inhibitory circuits (Chambers et al., 2003). Alternatively, adolescents may be particularly motivated by the potential for immediate reinforcement. For example, the maturation of the caudate (a subdivision of the striatum, together with the putamen) is delayed in children with disorders characterized by delayed gratification deficits (Castellanos et al., 2002).

3.2.2.3. Dopaminergic activity. Dopaminergic activity makes a considerable contribution to changes in prefrontal-striatal-limbic pathways (i.e., reward system) during adolescence. The peak observed during adolescence or early adulthood, which declines thereafter, predicts the increase in exploratory, risk-taking behaviour, and thus in reward-seeking, which cannot yet be controlled by the immature frontal regions (Wahlstrom et al., 2010). When Steinberg (2010) measured risky behaviours using laboratory paradigms, they reported a peak in performance at around 15 years. As suggested by Steinberg (2010), this temporal disjunction exerts a favourable influence from a developmental point of view. However, studies conducted on late adolescence, comparing adolescents with young adults, are too sparse for us to pinpoint the subsequent decline in risk-taking behaviours. Moreover, some individuals are more vulnerable to the potentially negative consequences of this neurobehavioural shift than others and their neural responses to rewards may be different. For instance, individuals whose genetic predispositions result in higher levels of dopamine in neural synapses, particularly in circuits involved in reward processing, demonstrate increased levels of brain activation in response to rewards (Dreher et al., 2009; Hariri, 2009). However, there are not yet any converging data on these predispositions, which may also stem from negative experiences in infancy or early childhood. Some studies, for instance, have reported contradictory data about the maturation of WM and risk-taking (Berns et al., 2009; Olson et al., 2009). Social, environmental and educational factors may also contribute to this heterogeneity, in addition to maturational ones. Hence, further studies are essential if we are to understand these apparent inconsistencies.

4. Discussion

The results of neuroimaging studies are consistent with the main concepts of psychoanalysis on adolescence, namely a transition to adulthood with a more integrated self and the development of social skills. Laboratory studies have shown that adolescents generally have a greater risk-taking propensity than adults, although there is considerable interindividual variability. While ignorance of the actual level of risk cannot be a major factor in risk-taking by typically developing adolescents, given that their knowledge of the risks is roughly similar to that of their elders (Furby and Beyth-Marom, 1992; Klaczynski, 2004), sensation-seeking and, above all, sensitivity to the peer group do seem to play an important role, unlike in adults. As stated by Winnicott, adolescents need to gain experience of life, if they are to learn how to live and, more especially, if they are to find out whether life is worth living. They must abandon many of the childhood certainties, including the feeling of being protected by their parents, and must also de-idealize the latter. This teleological conception of action has been taken up by several researchers in the cognitive field, who see risk-taking as an adaptive mechanism allowing certain cortical structures to be optimised, particularly those involved in social cognition.

However, several important concepts specific to psychoanalysis are not used as tools for analysing action. This is particularly true of "drive", including sex drive, which can in no way be reduced to the concept of "motivation". Furthermore, the psychoanalytic approach focuses on cathexis. As stated by Erikson (1956), the cure process emerges amid the integration of diverse elements of personal experience, such as identity and intimacy, the past and the present, and the world of internal object representations and external relationships. Adolescents may sometimes modify the way they relate to the world through their experience of the course of treatment and through transference.

Neuroscience research tends to isolate the mechanisms of action and seek out their brain substrates. As this information does not arise from an individual's own experience, unlike that relating to a psychoanalytic cure, he or she cannot directly take this knowledge on board and integrate it into his or her psychic functioning. It can therefore be useful only as an external constraint: for example, the training, medication, or even electrical stimulation that is sometimes offered in cases of depression or addiction. Psychoanalytic referents and processes would appear to be useful tools for decoding behaviours, and possibly for modifying them at the risk-taking stage. They are, however, of little or no direct use at the addictive stage.

5. Conclusion

Psychoanalytic concepts of risk-taking in adolescents are supported by the findings of brain development studies. Risk-taking promotes the exploration of adult roles, may increase self-esteem (see Hoge and McCarthy, 1984), and promotes reproductive success. Risk-taking contributes to the efficient shaping of the most highly evolved parts of the brain that are responsible for the "sapience" which characterizes the human species.

The interrelations between cognition and emotion remain relatively poorly understood, and the study of adolescent brain development would appear to offer the best conditions for studying them. Neuroimaging studies have shown that neural circuitry undergoes major reorganization during adolescence, particularly in those regions of the brain relating to executive functions, the self and social cognition, and that the "emotional brain" may play a role in that reorganization.

References

Alexander, C.S., Kim, Y.J., Ensminger, M., Johnson, K.E., Smith, B.J., Dolan, L., 1990. A measure of risk taking for young adolescents: reliability and validity assessments. J. Youth Adolescence 19 (6), 559–569.
Arnett, J., 1992. Reckless behavior in adolescence: a developmental perspective. Dev. Rev. 12 (4), 339–373.
Bauman, A., Phongsavan, P., 1999. Epidemiology of substance use in adolescence: prevalence, trends and policy implications. Drug Alcohol Depen. 55, 187–207.
Berns, G.S., Moore, S., Capra, C.M., 2009. Adolescent engagement in dangerous behaviors is associated with increased white matter maturity of frontal cortex. PLoS One 4 (8), e6773.
Beyth-Marom, R., Austin, L., Fischoff, B., Palmgren, C., Jacobs-Quadrel, M., 1993. Perceived consequences of risky behaviors: adults and adolescents. Dev. Psychol. 29, 549–563.
Blos, P., 1958. Preadolescent drive organization. J. Am. Psychoanal. Assoc. 6, 47–56.
Blos, P., 1962. On adolescence: A psychoanalytic interpretation. Free Press of Glencoe, New York.

Blos, P., 1967. The second individuation process of adolescence. Psychoanal. St. Child 22, 162–186.
Blos, P., 1980. The life cycle as indicated by the nature of the transference in the psychoanalysis of adolescents. Int. J. Psycho-Anal. 61, 145–151.
Blos, P., 1989. The place of the adolescent process in the analysis of the adult. Psychoanal. St. Child 44, 3–18.
Bornstein, R.F., 2005. Reconnecting psychoanalysis to mainstream psychology: challenges and opportunities. Psychoanal. Psychol. 22, 323–340.
Brook, J.S., Balka, E., Whiteman, M., 1999. The risks for late adolescence of early adolescent marijuana use. Am. J. Public Health 89, 1549–1554.
Casey, B.J., Getz, S., Galvan, A., 2008. The adolescent brain. Dev. Rev. 28, 62–77.
Castellanos, F.X., Lee, P.P., Sharp, W., Jeffries, N.O., Greenstein, D.K., Clasen, L.S., Blumenthal, J.D., James, R.S., Ebens, C.L., Walter, J.M., Zijdenbos, A., Evans, A.C., Giedd, J.N., Rapoport, J.L., 2002. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA 288 (14), 1740–1748.
Cauffman, E., Steinberg, L., 2000. (Im)maturity of judgment in adolescence: why adolescents may be less culpable than adults. Behav. Sci. Law 18 (6), 741–760.
Chambers, R.A., Taylor, J.R., Potenza, M.N., 2003. Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. Am. J. Psychiat. 160, 1041–1052.
Degenhardt, L., Chiu, W.T., Sampson, N., Kessler, R.C., Anthony, J.C., Angermeyer, M., Bruffaerts, R., de Girolamo, G., Gureje, O., Huang, Y., Karam, A., Kostyuchenko, S., Lepine, J.P., Mora, M.E., Neumark, Y., Ormel, J.H., Pinto-Meza, A., Posada-Villa, J., Stein, D.J., Takeshima, T., Wells, J.E., 2008. Toward a global view of alcohol, tobacco, cannabis, and cocaine use: findings from the WHO World Mental Health Surveys. PLoS Med. 5 (7), e141.
Dreher, J.C., Kohn, P., Kolachana, P., Weinberger, D.R., Berman, K.F., 2009. Variation in dopamine genes influences responsivity of the human reward system. Proc. Natl. Acad. Sci. USA 106 (2), 617–622.
Durston, S., Thomas, K.M., Yang, Y., Ulug, A., Zimmerman, R., Casey, B.J., 2002. A neural basis for the development of inhibitory control. Dev. Sci. 5, 9–16.
Elliott, R., Dolan, R.J., Frith, C.D., 2000. Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. Cereb. Cortex.
Erikson, E.H., 1956. The problem of ego identity. J. Am. Psychoanal. Assoc. 4, 56–121.
Ernst, M., Nelson, E.E., Jazbec, S., McClure, E.B., Monk, C.S., Leibenluft, E., Blair, J., Pine, D.S., 2005. Amygdala and nucleus accumbens activation in response to receipt and omission of gains in adults and adolescents. Neuroimage 25, 1279–1291.
Freud, S., 1985. In: Masson, J.M. (Ed.), The Complete Letters of Sigmund Freud to Wilhelm Fliess, 1887–1904. Harvard University Press, Cambridge, pp. 287–289.
Freud, S., 1900. The Interpretation of Dreams. Avon, New York. pp. 1980.
Freud, S., 1905. Three Essays on the Theory of Sexuality. Basic Books, New York. pp. 123–243.
Freud, S., 1912. On the Universal Tendency to Debasement in the Sphere of Love (Contributions to the Psychology of Love II). The Standard Edition of the Complete Psychological Works of Sigmund Freud, Volume XI (1910): Five Lectures on Psycho-Analysis, Leonardo da Vinci and Other Works, pp. 177–190.
Freud, S., 1927. The Future of an Illusion. The Standard Edition of the Complete Psychological Works of Sigmund Freud, Volume XXI (1927–1931): The Future of an Illusion, Civilization and its Discontents, and Other Works. Hogarth Press, London, pp. 1–56.
Furby, L., Beyth-Marom, R., 1992. Risk taking in adolescence: a decision-making perspective. Dev. Rev. 12, 1–44.
Gaddini, E., 1992. In: Limentani, A. (Ed.), A Psychoanalytic Theory of Infantile Experience. Routledge, London.
Galvan, A., Hare, T., Parra, C., Penn, J., Voss, H., Glover, G., Casey, B.J., 2006. Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. J. Neurosci. 26, 6885–6892.
Galvan, A., Hare, T., Voss, H., Glover, G., Casey, B.J., 2007. Risk-taking and the adolescent brain: who is at risk? Dev. Sci. 10, F8–F14.
Gardner, W., Herman, J., 1991. Adolescents' AIDS risk taking: a rational choice perspective. In: Gardner, W., Millstein, S., Wilcox, B. (Eds.), Adolescents in the AIDS Epidemic. Jossey-Bass, San Francisco, pp. 17–34.
Gardner, M., Steinberg, L., 2005. Peer influence on risk taking, risk preference, and risky decision making in adolescence and adulthood: an experimental study. Dev. Psychol. 41, 625–635.
Giorgio, A., Watkins, K.E., Chadwick, M., James, S., Winmill, L., Douaud, G., De Stefano, N., Matthews, P.M., Smith, S.M., Johansen-Berg, H., James, A.C., 2010. Longitudinal changes in grey and white matter during adolescence. Neuroimage 49, 94–103.
Glover, E., 1932a. Common problems in psychoanalysis and anthropology: drug ritual and addiction. Brit. J. Med. Psychol. 12, 109–131.
Glover, E., 1932b. On the aetiology of drug-addiction. Int. J. Psycho-Anal. 13, 298–328.
Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D., Vaituzis, A.C., Nugent 3rd, T.F., Herman, D.H., Clasen, L.S., Toga, A.W., Rapoport, J.L., Thompson, P.M., 2004. Dynamic mapping of human cortical development during childhood through early adulthood. Proc. Natl. Acad. Sci. USA 101, 8174–8179.
Hare, T.A., Tottenham, N., Galvan, A., Voss, H.U., Glover, G.H., Casey, B.J., 2008. Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. Biol. Psychiat. 63 (10), 927–934.
Hariri, A.R., 2009. The neurobiology of individual differences in complex behavioral traits. Annu. Rev. Neurosci. 32, 247–255.
Hoge, D.R., McCarthy, J.D., 1984. Influence of individual and group identity salience in the global self-esteem of youth. J. Pers. Soc. Psychol. 47 (2), 403–414.
Hopper, E., 1981. Forms of instrumental adjustment. In: Social Mobility: A Study of Social Control and Insatiability. Blackwell, Oxford, pp. 225–241.
Johnson, B., 1999. Three perspectives on addiction. J. Am. Psychoanal. Assoc. 47, 791–881.
Johnson, J.G., Cohen, P., Pine, D.S., Klein, D.F., Kasen, S., Brook, J.S., 2000. Association between cigarette smoking and anxiety disorders during adolescence and early adulthood. JAMA 284 (18), 2348–2351.
Johnston, L.D., O'Malley, P.M., Bachman, J.G., Schulenberg, J., 2007. Monitoring the Future National Survey Results on Drug Use, 1975–2006, vol. II.
Kapusta, N.D., Plener, P.L., Schmid, R., Thau, K., Walter, H., Lesch, O.M., 2007. Multiple substance use among young males. Pharmacol. Biochem. Behav. 86, 306–311.
Khantzian, E.J., 1997. The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. Harv. Rev. Psychiat. 4 (5), 231–244 (review).
Klaczynski, P.A., 2004. A dual-process model of adolescent development: implications for decision making, reasoning, and identity. Adv. Child Dev. Behav. 32, 73–123 (review).
Knutson, B., Fong, G.W., Adams, C.M., Varner, J.L., Hommer, D., 2001a. Dissociation of reward anticipation and outcome with event-related fMRI. Neuroreport 12 (17), 3683–3687.
Knutson, B., Adams, C.M., Fong, G.W., Hommer, D., 2001b. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J. Neurosci. 21 (16).
Krystal, H., 1982. Adolescence and the tendencies to develop substance dependence. Psychoanal. Inq. 2, 581–617.
Laviola, G., Adriani, W., Terranova, M.L., Gerra, G., 1999. Psychobiological risk factors for vulnerability to psychostimulants in human adolescents and animal models. Neurosci. Biobehav. Rev. 23 (7), 993–1010.
Lebel, C., Walker, L., Leemans, A., Phillips, L., Beaulieu, C., 2008. Microstructural maturation of the human brain from childhood to adulthood. Neuroimage 40 (3), 1044–1055 (Epub 2008).
Lenroot, R.K., Giedd, J.N., 2010. Sex differences in the adolescent brain. Brain Cogn. 72 (1), 46–55.
Lenroot, R., Gogtay, N., Greenstein, D., Wells, E., Wallace, G., Clasen, L., Blumenthal, J.D., Lerch, J., Zijdenbos, A.P., Evans, A.C., Thompson, P.M., Giedd, J.N., 2007. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. Neuroimage.
Liston, C., Watts, R., Tottenham, N., Davidson, M.C., Niogi, S., Ulug, A.M., Casey, B.J., 2006. Frontostriatal microstructure modulates efficient recruitment of cognitive control. Cereb. Cortex 16 (54), 553–560.
Luna, B., Thulborn, K.R., Munoz, D.P., Merriam, E.P., Garver, K.E., Minshew, N.J., Keshavan, M.S., Genovese, C.R., Eddy, W.F., Sweeney, J.A., 2001. Maturation of widely distributed brain function subserves cognitive development. Neuroimage 13, 786–793.
Monk, C.S., McClure, E.B., Nelson, E.E., Zarahn, E., Bilder, R.M., Leibenluft, E., Charney, D.S., Ernst, M., Pine, D.S., 2003. Adolescent immaturity in attention-related brain engagement to emotional facial expressions. Neuroimage 20 (1), 420–428.
Monk, C.S., Telzer, E.H., Mogg, K., Bradley, B.P., Mai, X., Louro, H.M.C., Chen, G., McClure-Tone, E.B., Ernst, M., Pine, D.S., 2008. Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. Arch. Gen. Psychiat. 65, 568–576.
Naqvi, N.H., Bechara, A., 2009. The hidden island of addiction: the insula. Trends Neurosci. 32 (1), 56–67.
Olson, E.A., Collins, P.F., Hooper, C.J., Muetzel, R., Lim, K.O., Luciana, M., 2009. White matter integrity predicts delay discounting behavior in 9- to 23-year-olds: a diffusion tensor imaging study. J. Cogn. Neurosci. 21 (7), 1406–1421.
Overton, W., 1990. Competence and procedures: constraints on the development of logical reasoning. In: Overton, W. (Ed.), Reasoning, Necessity, and Logic: Developmental Perspectives. Erlbaum, Hillsdale, NJ, pp. 1–32.
Palmer, R.H.C., Young, S.E., Hopfer, C.J., Corley, R.P., Stallings, M.C., Crowley, T.J., Hewitt, J.K., 2009. Developmental epidemiology of drug use and abuse in adolescence and young adulthood: evidence of generalized risk. Drug Alcohol Depen. 102 (1–3), 78–87.
Perrin, J.S., Hervé, P.Y., Leonard, G., Perron, M., Pike, G.B., Pitiot, A., Richer, L., Veillette, S., Pausova, Z., Paus, T., 2008. Growth of white matter in the adolescent brain: role of testosterone and androgen receptor. J. Neurosci. 28 (38), 9519–9524.
Perrin, J.S., Leonard, G., Perron, M., Pike, G.B., Pitiot, A., Richer, L., Veillette, S., Pausova, Z., Paus, T., 2009. Sex differences in the growth of white matter during adolescence. Neuroimage 45 (4), 1055–1066.
Reppucci, N.D., 1999. Adolescent development and juvenile justice. Am. J. Commun. Psychol. 27 (3), 307–326.
Riggs, N.R., Chou, C.P., Li, C., Pentz, M.A., 2007. Adolescent to emerging adulthood smoking trajectories: when do smoking trajectories diverge, and do they predict early adult nicotine dependence? Nicotine Tob. Res. 9 (11), 1147–1154.
Ritvo, S., 1971. Late adolescence—developmental and clinical considerations. Psychoanal. St. Child 26, 241–263.
Schmithorst, V.J., Wilke, M., Dardzinski, B.J., Holland, S.K., 2005. Cognitive functions correlate with white matter architecture in a normal pediatric population: a diffusion tensor MRI study. Hum. Brain Mapp. 26 (2), 139–147.
Schmithorst, V.J., Holland, S.K., Dardzinski, B.J., 2008. Developmental differences in white matter architecture between boys and girls. Hum. Brain Mapp. 29 (6), 696–710.

Segal, H., 1957. Notes on symbol formation. Int. J. Psychoanal. 38, 391–397.
Shaw, P., Lerch, J., Greenstein, D., Sharp, W., Clasen, L., Evans, A., Giedd, J., Castellanos, F.X., Rapoport, J., 2006. Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. Arch. Gen. Psychiat. 63 (5), 540–549.
Silveri, M.M., Tzilos, G.K., Pimentel, P.J., Yurgelun-Todd, D.A., 2006. Trajectories of adolescent emotional and cognitive development: effects of sex and risk for drug use. Ann. NY Acad. Sci. 1021, 363–370.
Sowell, E.R., Delis, D., Stiles, J., Jernigan, T.L., 2001a. Improved memory functioning and frontal lobe maturation between childhood and adolescence: a structural MRI study. J. Int. Neuropsychol. Soc. 7, 312–322.
Sowell, E.R., Thompson, P.M., Tessner, K.D., Toga, A.W., 2001b. Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: inverse relationships during postadolescent brain maturation. J. Neurosci. 21 (22), 8819–8829.
Spear, L.P., 2000. The adolescent brain and age-related behavioral manifestations. Neurosci. Biobehav. Rev. 24, 417–463.
Spear, L.P., 2002. The adolescent brain and the college drinker: biological basis of the propensity to use and misuse alcohol. J. Stud. Alcohol (Suppl. 14), 71–81.
Steinberg, L., 2004. Risk-taking in adolescence: what changes, and why? Ann. NY Acad. Sci. 1021, 51–58.
Steinberg, L., 2008. A social neuroscience perspective on adolescent risk-taking. Dev. Rev. 28, 78–106.
Steinberg, L., 2010. A dual systems model of adolescent risk-taking. Dev. Psychobiol. 52 (3), 216–224.
Steinberg, L., Cauffman, E., 1996. Maturity of judgment in adolescence: psychosocial factors in adolescent decision making. Law Hum. Behav. 20, 249–272.
Steinberg, L., Silverberg, S.B., 1986. The vicissitudes of autonomy in early adolescence. Child Dev. 57, 841–851.
Stevens, M.C., Kiehl, K.A., Pearlson, G.D., Calhoun, V.D., 2007. Functional neural networks underlying response inhibition in adolescents and adults. Behav. Brain Res. 181 (1), 12–22.
Stuss, D.T., Alexander, M.P., 2007. Is there a dysexecutive syndrome? Philos. Trans. Roy. Soc. London B Biol. Sci. 362 (1481), 901–915 (review).
Tamm, L., Menon, V., Reiss, A.L., 2002. Maturation of brain function associated with response inhibition. J. Am. Acad. Child Adolescence Psychiat. 41 (10), 1231–1238.
Tamnes, C.K., Ostby, Y., Walhovd, K.B., Westlye, L.T., Due-Tønnessen, P., Fjell, A.M., 2010. Intellectual abilities and white matter microstructure in development: a diffusion tensor imaging study. Hum. Brain Mapp..
Van De Ven, M.O., Greenwood, P.A., Engels, R.C., Olsson, C.A., Patton, G.C., 2010. Patterns of adolescent smoking and later nicotine dependence in young adults: a 10-year prospective study. Public Health 124 (2), 65–67 (Epub 2010).
Wagner, F.A., Anthony, J.C., 2002. From first drug use to drug dependence: developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. Neuropsychopharmacology 26 (4), 479–488.
Wahlstrom, D., Collins, P., White, T., Luciana, M., 2010. Developmental changes in dopamine neurotransmission in adolescence: behavioral implications and issues in assessment. Brain Cogn. 72 (1), 146–159.
Wechsler, H., Kuo, M., 2000. College students define binge drinking and estimate its prevalence: results of a national survey. J. Am. Coll. Health 49 (2), 57–64.
White, T., Su, S., Schmidt, M., Kao, C.Y., Sapiro, G., 2010. The development of gyrification in childhood and adolescence. Brain Cogn. 72 (1), 36–45 (Epub 2009 November 25 review).
Winnicott, D.W., 1965. The maturational processes and the facilitating environment: studies in the theory of emotional development. Int. Psychoanal. Library 64, 1–276.
Winters, K.C., Stinchfield, R.D., Lee, S., Latimer, W.W., 2008. Interplay of psychosocial factors and the long-term course of adolescents with a substance use disorder. Subst. Abus. 29 (2), 107–119.
Wood, J.N., Romero, S.G., Knutson, K.M., Grafman, J., 2005. Representation of attitudinal knowledge: role of prefrontal cortex, amygdala and parahippocampal gyrus. Neuropsychologia 43 (2), 249–259.
Zinberg, N., 1975. Addiction and ego function. Psychoanal. Study Child 30, 567–588.

Adolescent Health and the Environment

Mari S. Golub

California Regional Primate Research Center, University of California Davis, Davis, California, USA

The effects of toxicants depend on the dose and the time in the life span when exposure occurs. The biology of adolescence is distinctive and provides opportunities for unique actions of toxicants both in terms of disruption of function and disruption of maturation. Maturation of a number of organ systems occurs during this period, including not only the reproductive system but also the respiratory, skeletal, immune, and central nervous systems. Adolescence is a time of increased risk for infectious disease and accidental injury, making the effects of toxicants on the immune and central nervous systems particularly harmful. Differences in blood volume, respiratory parameters, metabolic needs, and capacity all contribute to altered pharmacokinetics. Exposures can also change. Increased food intake associated with rapid adolescent growth alters exposure to food contaminants. Voluntary drug consumption increases, including drinking; smoking; substance abuse; and the use of over-the-counter, prescription, and performance-enhancing drugs. At the same time, adolescents are introduced to toxicants in the workplace. Basic research in the toxicology of adolescence needs to take into account the appropriateness of animal models for this distinctive human developmental stage; risk assessment must take into account pharmacokinetic and lifestyle factors. Screening methodologies that would identify toxic effects unique to adolescence would also be valuable. *Key words* adolescence, animal, exposure, health effects, human, postnatal, puberty. *Environ Health Perspect* 108:355–362 (2000). [Online 6 March 2000]

http://ehpnet1.niehs.nih.gov/docs/2000/108p355-362golub/abstract.html

Recently there has been concern in the risk assessment community about the potentially greater susceptibility of children to environmental toxicants (*1–3*). In these documents, "children" refers to neonates through 18-year-olds. Although progress has been made in understanding and preventing risk at earlier stages of development, less is known about the later stages and, in particular, the final stage of maturation (adolescence). Adolescence is a fascinating period in terms of both its biology and its unique contributions to competent human adult functioning. The toxicology of adolescence needs to take into account both the biology and the function of this developmental period.

Literature on adolescent toxicology does not yet exist. Further, key words related to adolescent development are infrequently provided by the authors of toxicology studies. Thus, this review attempts to provide more general information about adolescence that may be valuable in considering risks to adolescent health due to exposure to environmental toxicants.

"Adolescence" is a term that has no precise biologic definition. It most often applies to humans, and it usually refers to the period from the appearance of secondary sex characteristics to the attainment of adult height (being "grown-up") at roughly 11–19 years of age (*4,5*). The term "puberty" is usually restricted to sexual maturation and refers to the onset of reproductive function.

Major Health Problems of Adolescence

The mortality rate in adolescence is low as compared to other periods of the life span. In 1996, the major causes of adolescent mortality in the United States, using U.S. health statistics categories, were injury (including accidents, homicide, and suicide), cancer, heart disease, and acquired immunodeficiency syndrome (*6*). Major sources of morbidity are infectious disease, particularly sexually transmitted disease, and substance abuse. This same pattern is seen in developing countries as pediatric care improves, marriage is postponed, and a pattern of urban migration for employment is established in young people. Although morbidity and mortality are relatively low, some types of disease show a peak incidence in the adolescent years. The highest incidence of hepatitis (*7*) and infections of the gastrointestinal tract (*8*) have been noted in the adolescent age range. The highest rate of near-fatal asthma attacks occurs in adolescence (*9*). Midadolescence is the peak time for the onset of eating disorders (*10*). Pathologic sleep conditions such as sleep apnea and delayed sleep phase syndrome have their symptomatic onset in adolescence (*11*). In addition, adolescence is a time of symptomatic emergence for diseases that are largely dormant in childhood, including diabetes, thyroid disorders, coronary artery disease, schizophrenia, and autoimmune disease. Public health focus is typically on reducing injury risk behaviors; promoting reproductive health (safe sex); and preventing pregnancy, substance abuse, and dropping out of school (*12*). Environmental exposures are rarely mentioned as a subject of concern or intervention.

Disorders of timing of maturation are one subject of concern that has been linked to environmental exposures (*13,14*). In particular, precocious puberty and the early appearance of secondary sex characteristics in girls have been attributed to contaminants with estrogenic properties (*15,16*). Delayed puberty and inadequate pubertal growth are thought to have strong environmental as well as genetic determinants, although the effects of chemicals in the environment have not been widely investigated (*17*).

Several authors have proposed that early and late puberty are risk factors for later adult disorders, particularly brain dysfunction. Over the years, differences in cognitive ability (*18,19*) and susceptibility to psychopathology (*20–22*) have been attributed to early and late maturers. Influential hypotheses have been advanced concerning the role of delayed or faulty adolescent brain maturation in the etiology of schizophrenia (*22–24*), and some direct evidence has been presented (*25,26*). These hypotheses are prompted by evidence that neural substrates implicated in schizophrenia mature during adolescence (*27*). Other outcomes for which age at puberty may be a risk factor include short stature (*28*), obesity (*29*), breast cancer (*30,31*), and polycystic ovary syndrome (*32*).

Finally, the regression of clinical problems at adolescence bears consideration. A small body of research has also developed to investigate the regression of symptomatology of hyperactivity, attention deficit disorders, and minimal brain dysfunction syndromes at

Address correspondence to M.S. Golub, California Regional Primate Research Center, University of California Davis, Davis, CA 95616 USA. Telephone: (530) 752-5119. Fax: (530) 752-2880. E-mail: msgolub@ucdavis.edu

Supported by NIH grants ES04190 and RR00169 and U.S. EPA grant R 827404.

Received 13 July 1999; accepted 30 September 1999.

ED_001854_00010735-00001

the time of puberty (*33,34*). Several interesting hypotheses concerning the role of growth factors (*35*) and steroid hormones have been proposed. Thus, failure of the normal pattern of symptom regression in these disorders could also be a consequence of environmental toxicant exposure.

Factors That Influence Toxicant Exposure and Effects

Exposure to environmental toxicants can be altered as a consequence of introduction into new environments; altered food, water, and air intakes; and physiologic changes that influence toxicokinetics.

Situational changes. Initiation of drinking and smoking and experimentation with recreational drugs are hallmarks of adolescence. The National Institute on Drug Abuse conducts a yearly survey of drug, alcohol, and tobacco use (*36*) with information for students in grades 8, 10, and 12. Data are provided in terms of prevalence; in 1998, the percentage of children who had ever used an illegal drug (including inhalants) was 38, 49, and 56% for grades 8, 10, and 12, respectively. Information on dose and frequency is not provided in this report. The initiation of oral contraception use, the use of anabolic steroids and other performance-enhancing drugs in athletics, and direct access to over-the-counter medications also occur in adolescence. Documentation of the extent of exposure in terms of dose, duration, and age groups affected is rarely available. In addition to potential direct harmful effects, many of these agents can secondarily influence environmental toxicant metabolism by inducing metabolic pathways.

Adolescents, when introduced to the workplace, may be exposed to chemicals in an occupational setting that has safeguards designed for adults. Here in the United States, the legal age for employment as an adult is 18, but younger children can work with some restriction (*37*). Workers 14–17 years of age are limited in the hours that they can work and are excluded from certain hazardous occupations; restrictions differ for children who are 14–15 and 16–17 years of age. Some of the restricted jobs involve the use of power tools, equipment, or motor vehicles, or involve physical danger such as mining, working with explosives, demolition, and roofing; it is not clear to what extent chemical exposure is taken into account in the designation of hazardous jobs for young workers. Separate laws govern agricultural employment (*38*). Children younger than 16 years of age are restricted from handling or applying pesticides labeled danger, poison, or warning, but they can be employed in harvesting after pesticide application. Rules are less restrictive for teenagers who work on family farms and in family businesses. Illegal employment of adolescents must also be taken into account (*39*).

Children younger than 14 years of age also work, according to a recent National Academy of Sciences report (*40*). During the school year, 30.6% of 12-year-olds and 36.9% of 13-year-olds report working. Information on work-related fatalities and nonfatal injuries is provided in the report, but there are no data on exposure to chemical toxicants. Indeed, the report discusses the possibility of long-term health effects of chemical exposures during developmental periods, and points out the absence of information in this area. Systematic research programs on human adolescent exposure to toxicants are needed to fill this gap.

Whether or not they are employed, adolescents are typically involved in various internships and apprenticeships in the workplace and in clubs with occupational themes, such as 4-H. The type of work children engage in at home can also change during adolescence and can involve broader chemical exposure. Information on exposures during these activities is limited.

Physiologic changes influencing pharmacokinetics. Adolescent-specific pharmacokinetic modeling is not commonly encountered in the toxicology literature. A number of compilations of human data on somatic growth, organ weights, and tissue composition extend into adolescent years, providing useful information for this effort (*41–44*). Similar compilations for common animal models would be useful; *Growth at Adolescence,* by Tanner (*45*), is a classic text on adolescent growth and sexual maturation that contains a valuable chapter on animals as well as extensive information on humans.

Some information is available on changes in hepatic metabolic pathways during adolescence, but implications for effects on toxicant activation/deactivation are not defined (*46,47*). The major changes involve cholesterol and steroid hormone-metabolizing enzymes in liver and reproductive organs (*48–50*). Because pubertal changes in these enzyme systems are sex dependent, they represent one of the systems potentially disrupted by toxicants with endocrine effects. It is not known whether exposure to exogenous substrates for these enzyme systems can influence their maturational time course and adult function.

Lung function parameters undergo a growth spurt similar to the sudden increase in adolescent height and weight (*51*). As is the case for other growth parameters, the growth spurt occurs earlier in girls (12 years of age) than in boys (14 years of age) and culminates in sex-differentiated levels of function seen in adults. The lung function growth spurt lags somewhat behind the body size growth spurt, indicating that exposures by inhalation could be reduced on a milligram-per-kilogram body weight basis at some stages of adolescence.

Growth and nutrition. The striking increases in food intake that occur in connection with adolescent growth are well known in humans and have been documented in animals, although this area has not been the subject of extensive scholarly activity. Increased food intake results in increased intake of food contaminants by humans and of increased doses of toxicants administered in the diet to laboratory animals. Acceleration of food intake does not necessarily correspond to growth and may precede or follow the adolescent growth spurt, resulting in altered intake of food contaminants on a body weight basis. In a recent 4-week study in mice, we found that food intake decreased by one-half between 42 and 70 days of age (puberty/adolescence), whereas body weight increased by 50% at the same time (*52*). As a result, the delivered dose of toxicant, which was a fixed concentration of the diet, was 211 mg/kg/day during the first week of the study and 138 mg/kg/day during the fourth week (a 35% change).

Energy utilization, as indexed by oxygen uptake, also shows distinct changes in the peripubertal years (*53*). These changes are not eliminated by simple body mass corrections. Extrapolations of toxicant impacts based on metabolic rate may need to be modified for adolescents.

Water intake at various ages has been studied in connection with risk assessment for water contaminants (*1*). Neither the amount of fluid intake nor the proportion derived from drinking water changed substantially from childhood to adolescence. A large change in sources of fluid intake was reported in postadolescents (> 20 years of age) because of increased coffee/tea consumption. The age for this transition may occur earlier in some cultural contexts and may change with contemporary trends.

Protein-calorie malnutrition and micronutrient deficiencies can appear during periods of rapid growth in early adolescence because of poor-quality diets (*54–56*). Such deficiencies could influence toxicant action in several ways. For example, antioxidant defense via glutathione is diminished in protein deficiencies and vitamin and trace element deficiencies promote oxidative damage due to reduced antioxidant enzyme activity. Essential trace element deficiencies trigger compensatory changes in expression of the metal-binding proteins transferrin and metallothionein. In addition to their physiologic roles in iron and zinc metabolism, transferrin binds aluminum and manganese and

ED_001854_00010735-00002

metallothionein binds cadmium, copper, mercury, and nickel. Thus the uptake, distribution, and intracellular disposition of these toxic metals could be enhanced.

Nutritional deficiencies are of particular concern when pregnancy occurs during the growth phase of adolescent development (*57*). Toxicants that interfere with nutrient uptake or utilization could further exacerbate this situation. Nutritional deficiencies in teenaged mothers have been implicated in the greater incidence of gastroschisis in their offspring (*58*).

Adolescent Maturation in Humans and Laboratory Animals

The growth spurt. A period of rapid growth occurs at different ages in boys and girls and is closely associated with pubertal events (*45,59*). Longitudinal data are important for quantitation of the growth spurt as a rate or velocity (*60*). Height growth is the most general manifestation, and distinct contributions from long bone and trunk growth have been demonstrated (*59*). Peak growth velocity may be a valuable end point for use in toxicologic studies.

The skull also enlarges in adolescence, showing a peak in growth velocity of longitudinal head circumference at 11 years of age in girls and 15 years of age in boys (*61*). Craniofacial growth and ossification and the final stages of dental eruption occur within limited age-defined time spans; the jaw and chin are the last facial elements to reach mature proportions (*62*).

Some believe that the adolescent growth spurt is characteristic of all primate species, whereas others believe that it is uniquely human (*63,64*). Whatever the case may be, pubertal growth patterns in most mammalian species do not show the rate discontinuities seen in humans and in nonhuman primates. As is the case for other developmental stages, the short life span of the rodent makes it difficult to detect changes in the rate of maturation. In particular, the extended juvenile period between weaning and sexual maturity in humans is not prominent, and the discontinuous growth pattern that leads to an adolescent growth spurt has not been clearly demonstrated.

The development of sex-differentiated morphology of body size and composition is an important aspect of adolescent growth. Laboratory animals differ widely in the emergence of sex-differentiated morphology at puberty. Body size and external genitalia are the most widely used markers. Nonhuman primates, such as rhesus monkeys, show strong body size differentiation, but less morphologic differentiation of body proportions and composition than humans.

Puberty; the onset of reproductive function. In humans, normative data for pubertal development are typically reported in terms of the Tanner (*60*) stages, which are based on the appearance and extent of breast and penile development and pubic and axial hair. The Tanner study examined British schoolchildren; norms have also been developed within some other national and ethnic populations. Variations in patterning within normal populations have also been analyzed (*65,66*). Age at menarche (the onset of menses), thelarche (the onset of breast development), and adrenarche (the appearance of axial hair) are sometimes used as discrete landmarks of pubertal maturation in girls. For boys, the age at first ejaculation or at the first voice break are infrequently used as landmarks. In addition, continuous quantitative measures of penis length or nipple growth are sometimes used (*67,68*). Various indices of pubertal development are generally correlated in human populations, but both the sequence of events and the rate of development can vary, and it is not known whether environmental toxicants would be likely to affect all aspects of puberty in a similar manner.

In laboratory rodents, the age at vaginal opening and preputial separation are standard landmarks of puberty. These measures are now recommended for inclusion in safety testing studies conducted according to U.S. Environmental Protection Agency (EPA) guidelines (*69*). A broader context for estimating the impact of environmental chemicals, particularly pesticides, on puberty should become available as more studies including these end points are conducted. However, the relationship of vaginal opening and preputial separation to human landmarks like menarche is not known. In nonhuman primates, the age at menarche is often used for females (nonhuman primates, like humans, have menstrual cycles). Nipple size and anogenital distance have been used as quantitative indices in female monkeys, and testis length has been used in male monkeys.

The transmitters, growth factors, and hormonal influences involved in functional maturation of the hypothalamic–pituitary–gonadal axis and the onset of puberty are gradually becoming known. Control of the onset of puberty has been widely studied in humans, rhesus monkeys, and sheep. These studies allow the elaboration of mechanism hypotheses for investigating the effects of toxicants on puberty. These hypotheses are vital for understanding the biologic plausibility of effects of environmental contaminants on puberty biomarkers and for generalization across doses and species.

The changes in the tract during adolescence are pervasive and profound. After the onset of cyclic gonadotrophin release in boys, sperm cycles are established, leading to expanded size and complexity of testes. In girls, the uterus increases in size and becomes anteverted, the uterine cavity is established, and epithelial secretory activities are initiated. External genitalia increase in size in both sexes, and the vaginal epithelium thickens and undergoes changes in pH and glycogen content. Quantitative information on age- and maturation-dependent changes in internal reproductive organs is generally not available but may increase with the widespread use of noninvasive imaging technologies (*13*).

Anisimov (*70*) suggested that high rates of cell proliferation during periods of rapid growth could differentially predispose organs to genotoxic carcinogens. Thus, cellular proliferation in the male and female reproductive tracts that occurs during adolescence could increase susceptibility to toxicant-induced reproductive tract cancers. A similar hypothesis has been advanced for xenoestrogens and breast cancer (*71*). Experiments designed to directly test this hypothesis have not yet been conducted.

In humans, there is a distinctive but highly variable stage of adolescent sterility, during which menstrual and hormonal cycles gradually mature into the adult form (*72*). During this time, polycystic ovary syndrome is often encountered in young women. Similarly, in boys, ejaculate parameters do not reach adult values until sometime after puberty. Testicular varicocele, a vascular disorder, can appear in young postpubertal males (*73*). Both polycystic ovaries and varicocele have ties to later infertility. By disrupting the establishment of complex interactions that result in mature ovulation and sperm production, toxicants can influence the incidence of these disorders.

Adverse pregnancy outcomes are more common in teenage pregnancies, and some birth defects are associated with young maternal age (*74*). Developmental toxicants might be expected to differ in their impact on pregnancy during adolescence as compared to adulthood, but I could not locate any empirical information on this issue.

Skeletal maturation. A period of rapid bone growth mineralization coincides with the adolescent growth spurt. The role of steroid and growth hormones has been documented. Recent studies indicate that peak bone mineralization rate occurs 12–18 months after peak height growth rate (*75*), and corresponds to the time of menarche in girls (*76*). Bone mineralization continues into the next decade, and peak mineralization is reached in the mid to late 20s in women (*77*). Diminished bone mass accrual during adolescence is a risk factor for the

ED_001854_00010735-00003

development of osteoporosis later in life (*78*). The adolescent period of rapid mineralization could be a target of toxicants that influence bone (e.g., cadmium and lead). Skeletal maturation is also reflected in epiphyseal closure of the long bones and of some areas of the axial skeleton, such as the iliac epiphysis. Clinical tools have been developed to quantify skeletal maturation in humans using radiographs (*79*) and, more recently, magnetic resonance imaging (MRI) (*80*) and DEXA (*81*). Evaluation of skeletal maturation using these noninvasive techniques could also provide useful biomarkers for adolescent development in larger laboratory animals. In contrast to primate species, rodents do not experience epiphyseal closure at the end of adolescence and continue to add body length throughout the life span. The evaluation of skeletal maturation in rodents usually involves biochemical measurement.

Thymic involution and reproductive tract immunity. Adequate immune defense is extremely important in the adolescent years, when many pathogens are first encountered through an expansion of environmental contacts and the initiation of sexual activity (*7*). Thus, exposure to toxicants that impair immune function can be particularly harmful because of the already high risk of infectious disease.

During adolescence, sex-dependent differences in immune response are established; females have generally more responsive immune systems and are more sensitive to immunotoxicants (*82*). Steroid hormones under the regulation of GnRH are considered responsible for immune system alterations in adolescence. The thymus is an estrogen target tissue. Estrogen receptors are found on lymphocyte precursors as well as on stromal cells. Gonadal hormones appear to provide a tonic inhibitory function on the thymus; gonadectomy in adulthood leads to an increase in thymic tissue, whereas estrogen can produce thymic involution. In addition, GnRH may have effects on immune function around the time of puberty that are not mediated by gonadal steroids.

The major maturational landmark in the immune system during adolescence is thymic involution, characterized by a dramatic decrease in thymic tissue mass, primarily involving the perivascular space (*83*), a decrease in the production of new thymocytes, and an increase in the $CD4^+/CD8^+$ ratio (*84*). Although direct observation of changes in thymus size and composition requires tissue sampling, peripheral markers are available. Studies in humans, generally bracketing adolescence (6–19 years of age), have shown major changes in peripheral lymphocyte subpopulations as determined with cell-surface markers (*85*). Also, during adolescence, changes in the reproductive tract occur in preparation for the establishment of vaginal mucosal immunity. Maturational changes in gut mucosal immunity may also occur, as reflected in a peak number of Peyer's patches in the adolescent years (*8*).

Immunotoxicants that induce thymic involution, such as diethylstilbestrol and tetrachlorodibenzo-*p*-dioxin, might be anticipated to interfere with adolescent maturational changes in the immune system that involve the thymus. However, studies specifically targeting adolescence as a vulnerable developmental stage are not available.

Brain and behavior. Adolescence is a time of rapid advance in cognitive skills and intense acquisition of new information that sets the stage for a productive adult life. Therefore, suboptimal brain function can have long-term consequences. The high risk of injury and of conduct disorder during adolescence also points to the importance of identifying toxicant exposures that can impair brain function. In addition, maturation processes could be disrupted, leading to permanent effects on central nervous system (CNS) structure and function. Because of the importance of behavior in health risks of adolescence, this review emphasizes adolescent brain development.

Increased capacity for complex and abstract thought develops in adolescence, and parallels have been drawn between the timing of the final stages of Piagetian cognitive development (formal operations) and electroencephalography (EEG) coherence parameters (*86*). Correlations between hormone levels and behavioral characteristics of adolescents (impulsivity, etc.) are characterized in the psychology literature (*87*). In general, however, well-defined relationships between cognitive development and brain maturation parameters have not been established.

The maturation of the cerebral cortex is the final event in brain development. Two concepts are currently important in guiding research in late cortical morphologic maturation: pruning and connectivity.

Pruning refers to the decrease in synaptic density from the peak levels reached in early childhood (9–18 months of age in children) and was first described by Huttenlocker (*88*) using histologic methods. Recent MRI studies showing decreases in cortical gray matter volume are consistent with this concept, as are studies showing decreases in cortical glucose metabolism (*89*). In rhesus monkeys, pruning during late brain maturation has been confirmed by Goldman-Rakic and collaborators (*90–93*) through their studies on cortical synaptogenesis from embryogenesis to adulthood. During the juvenile and adolescent stages, decreases in synaptic density continue in the cortex, culminating in late adolescence in adult morphology (*88*).

Connectivity refers to increased myelination of major intracortical commissures during adolescence, as observed in children by Yakovlev and Lecours (*94*) and Benes (*95*) using histologic methods. MRIs of human adolescent brains and, in particular, the corpus callosum, are generally supportive of increased myelination as a major maturational process in the cortex (*96*), as are magnetic resonance spectroscopy imaging studies showing increased phospholipid metabolism. Several adolescent changes in electrophysiologic measures [increases in EEG coherence (*97*), decreases in delta sleep time (*98*), and decreases in EEG latencies (*99*)] have been attributed to increased intracortical connectivity. Clear temporal relationships between morphologic and functional measures of late brain maturation have not been identified.

Recently, MRI scans that image and quantitate brain composition in terms of white and gray matter have provided a surrogate measure for increased myelination (white matter) and potentially of decreased neuropil (gray matter). Normative data are becoming available, and several studies have specifically targeted adolescence (*100,101*).

Because of intensive myelination, it might be anticipated that myelin toxicants would have greater effects during adolescence. However, studies of age-dependent effects of myelin toxicants have typically targeted earlier postnatal periods.

Sex-differentiated morphology of the brain is thought to be established during fetal life and infancy and develop into full expression at the time of puberty (*102*). Presumably hormonal factors controlling other secondary sex characteristics also orchestrate the change in the brain during adolescence, but the mechanisms are not completely understood (*103,104*). Most of these changes are limited to sexually dimorphic regions of the hypothalamus. Other differences are found in corpus callosum (*105*) and in the cell-packing density of the granular layer of the cortex (*104*). More recently, the effects of estrogen on brain morphology continuing into adulthood have been described. As research expands, progress should be made in understanding the distinct contribution of the adolescent period to sex-differentiated brain structure and function and mechanisms by which this contribution could be disrupted by toxicants that affect the endocrine and nervous systems.

Studies of synaptic pruning in sensory systems have uncovered the importance of *n*-methyl-D-aspartate (NMDA) receptors in differential strengthening of synapses in late maturing cortex; NMDA leads to excess pruning, whereas NMDA antagonists

ED_001854_00010735-00004

promote synaptic density (*106,107*). There is also some suggestion that NMDA receptors are maximally sensitive during adolescence (*108*), as first suggested by the finding that pseudopsychotic effects of ketamine are not present in children, but emerge after puberty. Noradrenergic systems have also been implicated in synaptic pruning and cortical connectivity (*109–112*) in infancy. Studies in adolescence are not available.

In 1983, Spear and Brake (*113*) brought attention to changes in dopaminergic systems during adolescence in a thorough review. The authors provided a characterization of periadolescent (30- to 40-day-old) rats in terms of their spontaneous behavior (in isolation and in social settings), their performance in structured learning situations, and their behavioral response to CNS active drugs. Their research characterized 28- to 38-day-old rats as exhibiting an increase in spontaneous motor activity and social behavior. In structured learning situations, both improved and poorer performance was identified, depending on the task. An integrative interpretation offered by the authors was that periadolescent rats excelled in simple situations where increased activity was an advantage, but showed deficits in more complex tasks where increased activity could be a disadvantage. Spear and Brake (*113*) also pointed out some interesting effects on stimulus and reward efficacy. Studies from their laboratories showed a reduced behavioral response to direct and indirect dopamine agonists and an increased response to dopamine antagonists. Similar effects were not noted for cholinergic and serotonergic drugs. The authors proposed that the onset of dopamine autoreceptor function in the mesolimbic dopamine system during adolescence might underlie these characteristics of adolescence in rats.

Dopamine receptor density, like that of other neurotransmitters, changes through late brain development in concert with synaptic overproduction and pruning (*114*). This theme has been further developed in more recent studies by Andersen et al. (*115–117*) and Teicher and et al. (*118,119*), who found transient overexpression of dopamine receptors in the two major subcortical dopamine systems (striatum and nucleus accumbens) around the time of puberty in rats. Others have reported confirmatory findings. Adolescent rats differ from adults in their response to CNS active drugs including, but not limited to, dopamine active agents (*113,120–122*). Age-related changes in dopamine receptor subtypes in cortical areas have also been shown in monkeys (*93,123*), although few time points in the adolescent period have been studied, and information on subcortical areas is limited to adults. Recently reported human data (*124*) also showed a transient overexpression of D2 receptors in cortex through late adolescence.

The extrapolation of findings on dopamine receptors from rats to humans may be difficult. There is evidence that autoreceptor regulation of dopamine systems varies by species. Whereas human and nonhuman primates express autoreceptors in nigral striatal pathways, rats express them in striatum but also in ventral tegmental projections to the limbic system (*125*).

No information was found concerning changes in central or peripheral cholinergic systems in adolescence. Such information could be valuable in forming hypotheses about pesticides that influence cholinesterase activity.

The general maturational trend in EEG in adolescence is toward less slow-wave activity (*99*) and greater coherence (*25*) and complexity (*126*). The event-related potential (ERP), the brain electrical response to discrete meaningful sensory stimuli, is one of the best-characterized brain function parameters that changes during adolescence.

The ERP has sex-dependent characteristics that emerge during adolescence (*127,128*). Females generally show larger amplitude and shorter latency visual, auditory, and olfactory ERPs (*129*). The largest sex differences are for olfactory ERP amplitude (*130*), corresponding to the superior performance of women in olfactory tasks. The most significant sex differences occur at 15–20 years of age, and involve later ERP components and novel and task-relevant stimuli (*129–131*). Courchesne (*132*) has argued that changes in amplitude and latency of various ERP components correspond to developmental changes in myelination and synapse density. In particular, the amplitude of the Nc component declines markedly from 10–15 years of age, corresponding to synaptic pruning in the frontal cortex. Girls with Turner's syndrome, a genetic disorder characterized by hypogonadism, fail to show the normal developmental changes in frequency and duration of Nc from 9–14 to 15–20 years of age (*133*).

A decrease in central processing time (the speed with which mental functions are performed) is related to lowered latency of ERPs. Response time during cognitive testing, a marker of central processing time, decreases systematically during adolescence in humans (*134*). The slope of linear decline changed exponentially from 6 to 17 years of age. Although there is no distinct discontinuous change in adolescence, disruption of the predicted rate of change could reflect abnormal brain maturation.

A dramatic transition to later bedtimes is a prominent feature of human adolescence (*135*). Changes in sleep EEG have also been documented in humans (*97,99,136*). The biologic (as opposed to psychologic or sociologic) basis of this phenomenon is supported by a similar finding in rhesus monkeys living in indoor cages with no changes in the physical or social environment during adolescence (*137*). Lengthening of the nocturnal activity period in rodents at puberty may be a related observation (*138*). There is also inconsistent information concerning changes in melatonin production at puberty (*135*).

Some Animal Studies of Adolescent Toxicology

Although pubertal/adolescent rodents are widely used in toxicology research, exposures usually begin, and many times end, before the pubertal/adolescent period. When chronic exposures begin during adolescence, end points are often not measured until late in the life span. Studies directed at adolescence most frequently assess the reproductive system, CNS, and growth.

Reproductive toxicity. Pubertal end points were included in studies of methoxychlor (MXC), a model environmental estrogen, but exposures were not limited to the periadolescent period. One study administered MXC before puberty and through mating trials in adulthood (*139*); early vaginal opening and impaired fertility were reported. Early vaginal opening was again found in a second study, when MXC was administered beginning in the fetal period and continuing through sexual maturation (*140*). Fertility was impaired in adulthood, although MXC administration was discontinued before mating trials.

Although exposures for the uterotrophic assay (*141*) are limited to the adolescent period, the intent is not to study puberty-specific actions of estrogenic agents, but to take advantage of the low endogenous estrogen levels in immature animals to simplify the assay. Nonetheless, the uterotrophic assay does point out the greater susceptibility of estrogen-dependent tissues to exogenous estrogenic influences before the onset of ovarian steroid production and negative feedback via the hypothalamus.

Vaginal opening and preputial separation, indices of pubertal acceleration/delay, are now commonly studied as part of EPA guideline multigeneration studies (*69*). Data gathered in this way do not provide information about the unique response of adolescents to toxicants because the exposures occur throughout development and are not limited to the pubertal period. One study was located using several estrogenic agents and evaluating vaginal opening (*142*), but most studies of this type begin exposure at or before weaning.

Cadmium effects on testes present an example of a male reproductive toxicant for

ED_001854_00010735-00005

which pubertal exposures have been compared to adult exposures. The pubertal male rat was generally less sensitive than the adult, presumably because effects were mediated though effects on hypothalamic luteinizing hormone regulation, which was not yet mature in the pubertal males (*143,144*).

Concern about teenage drinking has made alcohol one of the agents most studied for its effects on adolescence. Recent *in vivo* studies in pubertal female rats suggest that single or short-term oral alcohol administration blocks vaginal opening that is induced by *N*-methyl-DL-aspartic acid (*145*); baseline gonadotropin levels were not altered. Anderson et al. (*146*) evaluated the effects of alcohol on male reproductive tract development. Mice were allowed *ad libitum* access to a liquid diet containing 5% ethanol beginning at weaning through the pubertal period (49 days of age). Effects on the reproductive tract relative to controls included lower weight of testes and accessory organs; reduced sperm count, sperm motility, and sperm fertilization ability; and increased incidence of abnormal sperm. These effects were attributed to delayed reproductive tract maturation, because most parameters normalized when treatment was extended an additional 2 weeks.

CNS end points. Alcohol is also one of the most-studied agents in terms of CNS effects in adolescence. Some indication of differential susceptibility to the sedative effects of alcohol in adolescence comes from studies in rats. The duration of absence of the righting reflex and depression of locomotor activity (*147*) and reduction in core body (*148*) were less affected in adolescents than adults after intraperitoneal (ip) ethanol administration. Development of tolerance to these effects has also been studied in adolescent rats and mice. In general, tolerance to motor effects and reduction of body temperature were greater in adolescents than in adults (*148*). In studies of behavioral function, presession ip administration of ethanol impaired the acquisition of a spatial maze task in 30-day-old male rats. *In vitro* administration studies also demonstrated differential effects of ethanol on electrical activity in brain slices. In studies of hippocampal brain slices from rats, NMDA-mediated electrical responses were more influenced by the addition of ethanol to the media in slices from adolescents than in slices from adults.

In addition, induction of long-term potentiation, an electrical surrogate for memory formation, was affected by the addition of ethanol to the incubation medium of slices from 15- to 25-day-old rats, but not 70- to 100-day-old rats. This effect was thought to be related to differential expression of NMDA receptor subtypes during this period. In a behavioral study, no differences were found in alcohol effects on visual or olfactory tasks in 35- to 38- as compared to 60- to 70-day-old rats (*149*); additionally, no differences in alcohol effects were found on nonspatial learning and memory tasks. However, ethanol effects were detected on a spatial task in adolescent but not in adult rats.

Surprisingly, apart from recent abstracts, literature searches did not locate animal studies on nicotine effects in adolescence. In humans, literature on smoking in adolescence has been directed mainly at respiratory parameters (*150–152*).

Because of the participation of teenagers in agricultural activities, there is concern about special sensitivity to pesticides during this period. Age-dependent effects of pesticides have been studied, both in terms of mortality and neurotoxicity, usually by comparing newborn or weanling rats to older and younger rats (*1*). To date, no general pattern of altered sensitivity has been described (*153*).

Metal toxicants and the growth spurt. Lead is one of the most widely studied developmental toxicants, and weanling rats are a common model. Both reproductive maturation and pubertal growth have recently been studied in lead-exposed rats; however, although they included the pubertal period, exposures were initiated earlier in development (*154,155*). In an interesting series of experiments, Hammond et al. (*156–159*) investigated the mechanism by which pubertal growth retardation was induced by lead administration in weanling female rats. They concluded that a centrally mediated effect on appetite and food intake was responsible.

Recommendations

Basic concepts and data concerning adolescence as a vulnerable period for environmental influences are extremely scattered and difficult to locate. This review represents an attempt to introduce relevant literature on adolescence to those interested in environmental health issues. Additionally, the following recommendations are put forward for consideration:

- Identify adolescence as a distinct developmental period in children's health research. Determine priorities for data needs in the area of adolescent toxicology.
- Identify end point methodologies that are appropriate for inclusion in animal toxicology studies conducted in the adolescent period.
- Establish *in vivo* and *in vitro* models for determining hazards unique to adolescence.
- Identify exposure periods in test species for the study of toxicology in adolescence. Establish guidelines for consistently including or excluding postweaning sexually immature animals in standard toxicology study designs.
- Consider adolescent development when establishing workplace exposure standards.
- Bracket the adolescent period when collecting age-dependent exposure data in survey studies.
- Examine the potential contribution of immunotoxicants and neurotoxicants to the high incidence of infection and injury in adolescents.

Human and animal research in the area of adolescent toxicology will help to safeguard adolescents as they complete their developmental time course and enter adulthood.

References and Notes

1. National Research Council. Pesticides in the Diets of Infants and Children. Washington, DC:National Academy Press, 1993.
2. Goldman L. Chemicals and children's environment: what we don't know about risks. Environ Health Perspect (suppl 3)106:875–880 (1998).
3. Goldman L. Linking research and policy to ensure children's environmental health. Environ Health Perspect (suppl 3)106:857–862 (1998).
4. Dorland's Illustrated Medical Dictionary. 25th ed. Philadelphia:W.B. Saunders, 1994.
5. Watts E. Adolescent growth and development of monkeys, apes and humans. In: Nonhuman Primate Models for Human Growth and Development (Watts E, ed). New York:Alan R. Liss, 1985;41–65.
6. Peters K, Kochanck K, Murphy S. Deaths: Final Data for 1996. Hyattsville, MD:National Center for Health Statistics, 1998.
7. Meheus A. Risk of hepatitis B in adolescence and young adulthood. Vaccine 13:S31–S34 (1995).
8. Van Kruiningen H, Ganley L, Freda B. The role of Peyer's patches in the age-related incidence of Crohn's disease. J Clin Gastroenterol 25:470–475 (1997).
9. Martin A, Campbell D, Gluyas P, Coates J, Ruffin R, Roder D, Latimer K, Luke C, Frith P, Yellowlees P, et al. Characteristics of near fatal asthma in childhood. Pediatr Pulmonol 20:1–8 (1995).
10. Stice E, Killen J, Hayward C, Taylor C. Age of onset for binge eating and purging during late adolescence: a 4-year survival analysis. J Abnorm Psychol 107:671–675 (1998).
11. Dahl R. The development and disorders of sleep. Adv Pediatr 45:73–90 (1998).
12. Schulenberg J, Maggs J, Hurrelman K. Health Risks and Developmental Transitions during Adolescence. Cambridge, UK:Cambridge University Press, 1997.
13. Hedlund G, Royal S, Parker K. Disorders of puberty: a practical imaging approach. Semin Ultrasound CT MRI 15:49–77 (1994).
14. Styne D. Puberty. In: Basic and Clinical Endocrinology (Greenspan FS, ed). Norwalk, CN:Appleton & Lange, 1991;519–542.
15. Hannon W, Hill RJ, Bernert JJ, Haddock L, Lebron G, Cordero J. Premature thelarche in Puerto Rico: a search for environmental estrogenic contamination. Arch Environ Contam Toxicol 16:255–262 (1987).
16. Herman-Giddens M, Slora E, Wasserman R, Bourdony C, Bhapkar M, Koch G, Hasemeier C. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. Pediatrics 99:505–512 (1997).
17. Delemarre-van de Waal HA. Environmental factors influencing growth and pubertal development. Environ Health Perspect 101(suppl 2):39–44 (1993).
18. Newcombe M, Dubas JS, Baenninger M. Associations of timing of puberty, spatial ability, and lateralization in adult women. Child Dev 60:246–254 (1989).
19. Nisbet JD, Illesley R. Influence of early puberty on test performance at age 11. Br J Educ Psychol 33:169–176 (1963).
20. Saugstad L. Age at puberty and mental illness. Towards

ED_001854_00010735-00006

a neurodevelopmental aetiology of Kraepelin's endogenous psychoses. Br J Psychiatry 155:536–544 (1989).
21. Saugstad L. Mental illness and cognition in relation to age at puberty: a hypothesis. Clin Genet 36:156–167 (1989).
22. Keshavan M, Anderson S, Pettegrew J. Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? The Feinberg hypothesis revisited. J Psychiatr Res 28:239–265 (1994).
23. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence. J Psychiatr Res 4:319–334 (1982).
24. Weinberger D. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 44:660–669 (1987).
25. Kaiser J, Gruzelier J. Timing of puberty and EEG coherence during photic stimulation. Int J Psychophysiol 21:135–149 (1996).
26. Galdos P, Van Os J, Murray R. Puberty and the onset of psychosis. Schizophr Res 10:7–14 (1993).
27. Lewis D. Development of the prefrontal cortex during adolescence: insights into vulnerable neural circuits in schizophrenia. Neuropsychopharmacology 16:385–398 (1997).
28. Albanese A, Stanhope R. Does constitutional delayed puberty cause segmental disproportion and short stature? Eur J Pediatr 152:293–296 (1993).
29. van Lenthe F, Kemper H, van Mechelen W. Rapid maturation in adolescence results in greater obesity in adulthood: the Amsterdam Growth and Health Study. Am J Clin Nutr 64:18–24 (1996).
30. Vihko R, Apter D. Endocrine characteristics of adolescent menstrual cycles: impact of early menarche. J Steroid Biochem 20:231–236 (1984).
31. Stoll B, Vatten L, Kvinnsland S. Does early physical maturity influence breast cancer risk? Acta Oncol 33:171–176 (1994).
32. Ibanez L, Potau N, Zampolli M, Street M, Carrascosa A. Girls diagnosed with premature pubarche show an exaggerated ovarian androgen synthesis from the early stages of puberty: evidence for gonadotropin-releasing hormone agonist testing. Fertil Steril 67:849–855 (1997).
33. Howell CD, Huessy HR, Hassuk B. Fifteen-year follow-up of a behavioral history of attention deficit disorder. Pediatrics 76:185–190 (1985).
34. Soorani-Lunsing R. Neurobehavioral relationships and puberty: another transformation. Early Hum Dev 34:59–67 (1993).
35. Rovet J, Netley C. The triple X chromosome syndrome in childhood. Child Dev 54:941–950 (1983).
36. Johnston C, O'Malley P, Bachman J. National Survey Results on Drug Use From the Monitoring the Future Study 1975–1997. Vol I: Secondary School Students. Rockville, MD:National Institute on Drug Abuse, 1998.
37. U.S. Department of Labor. Child Labor Requirements in Nonagricultural Occupations under the Fair Labor Standards Act (Child Labor Bulletin No. 101). Washington, DC:Employment Standards Administration Wage and Hour Division, 1990.
38. U.S. Department of Labor. Child Labor Requirement in Agriculture under the Fair Labor Standards Act (Child Labor Bulletin No. 102). Washington, DC:Employment Standards Administration Wage and Hour Division, 1984.
39. Kruse D, Mahoney D. Illegal Child Labor in the United States: Prevalence and Characteristics. Washington, DC:National Bureau of Economic Research, 1998.
40. Committee on the Health and Safety Implications of Child Labor, National Research Council and Institute of Medicine. Protecting Youth at Work: Health, Safety, and Development of Working Children and Adolescents in the United States. Washington, DC:National Academy Press, 1998.
41. Altman P, Dittmer D. Growth Including Reproduction and Morphological Development. Biological Handbooks. Washington, DC:FASEB, 1962.
42. White D, Widdowson E, Woodard H, Dickerson J. The composition of body tissues. 11: Fetus to young adult. Br J Radiol 64:149–159 (1991).
43. Tanner JM. Foetus into man: physical growth from conception to maturity. Cambridge, UK:Cambridge University Press, 1990.
44. Falkner F. Human Development. Philadelphia:W.B. Saunders Company, 1966.
45. Tanner J. Growth at Adolescence. Oxford:Blackwell Press, 1962.
46. Rogers A. The role of cytochrome P450 in developmental pharmacology. J Adolesc Health 15:635–640 (1994).
47. Capparelli E. Pharmacokinetic considerations in the adolescent: non-cytochrome P450 metabolic pathways. J Adolesc Health 15:641–647 (1994).
48. Vianello S, Waterman M, Dalla Valle L, Colombo L. Developmentally regulated expression and activity of 17 alpha-hydroxylase/C-17, 20-lyase cytochrome P450 in rat liver. Endocrinology 138:166–174 (1997).
49. Chang T, Bellward G. Peripubertal androgen imprinting of rat hepatic cytochrome P450 2C11 and steroid 5 alpha-reductase: pretranslational regulational and impact on microsomal drug activation. J Pharmacol Exp Ther 278:1383–1391 (1996).
50. Natarajan R, Ghosh S, Grogan W. Age-related changes in catalytic activity, enzyme mass, mRNA, and subcellular distribution of hepatic neutral cholesterol ester hydrolase in female rats. Lipids 32:463–470 (1997).
51. Wang X, Dockery D, Sypij D, Gold D, Speizer F, Ware J, Ferris BJ. Pulmonary function growth velocity in children 6 to 18 years of age. Am Rev Respir Dis 148:1502–1508 (1993).
52. Golub M, Keen C. Effects of dietary aluminum on pubertal mice. Neurobehav Toxicol Teratol 21:595–602 (1999).
53. Beunen G, Rogers D, Woynarowska B, Malina R. Longitudinal study of ontogenetic allometry of oxygen uptake in boys and girls grouped by maturity status. Ann Hum Biol 24:33–43 (1997).
54. Golub MS, Keen CL, Gershwin ME, Styne DM, Takeuchi PT, Ontell F, Walter RM, Hendrickx AG. Adolescent growth and maturation in zinc deprived rhesus monkeys. Am J Clin Nutr 64:274–282 (1996).
55. Golub M, Keen C, Gershwin M. Behavioral and hematological consequences of marginal iron-zinc nutrition in adolescent monkeys and the effects of a powdered beef supplement. Am J Clin Nutr 70:1059–1068 (1999).
56. Cai M, Yan WY. Study on iron nutritional status in adolescence. Biochem Environ Sci 3:113–119 (1990).
57. Naeye P. Teenage and preteenaged pregnancies: consequences of the fetal-maternal competition for nutrients. Pediatrics 67:146–150 (1981).
58. Torfs C, Lam P, Schaffer D, Brand R. Association between mothers' nutrient intake and their offspring's risk of gastroschisis. Teratology 58:241–250 (1998).
59. Tanner J, Whitehouse R, Marubini E, Resele L. The adolescent growth spurt of boys and girls of the Harpenden Growth Study. Ann Hum Biol 3:109–126 (1976).
60. Tanner J, Whitehouse R. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Arch Dis Child 51:170–179 (1976).
61. Epstein HT. Stages in human brain development. Dev Brain Res 30:114–119 (1986).
62. Graber T. Craniofacial and dentitional development. In: Human Development (Falkner F, ed). Philadelphia:W.B. Saunders Company, 1966;510–581.
63. Bogin B. Patterns of human growth. Cambridge, UK:Cambridge University Press, 1988.
64. Tardieu C. Short adolescence in early hominids: infantile and adolescent growth of the human femur. Am J Phys Anthropol 107:163–178 (1998).
65. Marshall W, Tanner J. Variations in pattern of pubertal changes in girls. Arch Dis Child 44:291–303 (1969).
66. Marshall W, Tanner J. Variations in the pattern of pubertal changes in boys. Arch Dis Child 45:13–23 (1970).
67. Aygun A, Akarsu S, Guvenc H, Kocabay K. Nipple and areola diameter in Turkish pubertal girls. J Adolesc Health 23:55–57 (1998).
68. Pokorny S, Murphy J, Preminger M. Circumferential hymen elasticity. A marker of physiologic maturity. J Reprod Med 43:943–948 (1998).
69. U.S. Environmental Protection Agency. Health Effect Test Guidelines. OPPTS 870.3800. Reproduction and Fertility Effects. Washington, DC:U.S. Government Printing Office, 1998.
70. Anisimov VN. Carcinogenesis and ageing. III: The role of age in initiation and promotion of carcinogenesis. Exp Pathol 22:131–147 (1982).
71. Ardies C, Dees C. Xenoestrogens significantly enhance risk for breast cancer during growth and adolescence. Med Hypotheses 50:457–464. (1998).
72. Lemarchand-Beraud T, Zufferey M, Reymond M, Rey I. Maturation of the hypothalamo-pituitary-ovarian axis in adolescent girls. J Clin Endocrinol Metab 54:241–246 (1982).
73. Belloli G, D'Agostino S, Zen F, Iovemo E. Fertility rates after successful correction of varicocele in adolescence and adulthood. Eur J Pediatr Surg 5:216–218 (1995).
74. Calzolari E, Bianchi F, Dolk H, Milan M. Omphalocele and gastroschisis in Europe: a survey of 3 million births 1980–1990. EUROCAT Working Group. Am J Med Genet 58:187–194 (1995).
75. Martin A, Bailey D, McKay H, Whiting S. Bone mineral and calcium accretion during puberty. Am J Clin Nutr 66:611–615 (1997).
76. McKay H, Bailey D, Mirwald R, Davison K, Faulkner R. Peak bone mineral accrual and age at menarche in adolescent girls: a 6-year longitudinal study. J Pediatr 133:682–687 (1998).
77. Teegarden D, Proulx W, Martin B, Zhao J, McCabe G, Lyle R, Peacok M, Slemenda C, Johnston C, Weaver C. Peak bone mass in young women. J Bone Miner Res 10:711–715 (1995).
78. Gilsanz V, Roe T, Mora S, Costin C, Goodman W. Changes in vertebral bone density in black girls and white girls during childhood and puberty. N Engl J Med 325:1597–1600 (1991).
79. Tanner J, Gibbons R. Automatic bone age measurement using computerized image analysis. J Pediatr Endocrinol 7:141–145. (1994).
80. Gabel G, Peterson HA, Berquistn T. Premature partial physeal arrest: diagnosis by magnetic resonance imaging in two cases. Clin Orthop 272:242–247 (1991).
81. Zanchetta J, Plotkin H, Alvarez Filgueira M. Bone mass in children: normative values for the 2–20-year-old population. Bone 16:393S–399S (1995).
82. Gaillard R, Spinedi E. Sex- and stress-steroids interactions and the immune system: evidence for a neuroendocrine-immunological sexual dimorphism. Domest Anim Endocrinol 15:345–352 (1998).
83. Steinmann G, Klaus B, Muller-Hermelink H. The involution of the ageing human thymic epithelium is independent of puberty. Scand J Immunol 22:563–575 (1985).
84. Hirokawa K, Utsuyama M, Dasai M, Kurashima C, Ishijima S, Zeng YX. Understanding the mechanism of the age-change of thymic function to promote T cell differentiation. Immunol Lett 40:269–277 (1994).
85. Utsuyama M, Hirokawa H, Kurashima C, Fukayama M, Inamatus T, Suzuki K, Hashimoto W, Satao K. Differential age-change in the number of $CD4^+CD45RA^+$ and $CD4^+CD29^+$ T cell subsets in human peripheral blood. Mech Aging Dev 63:57–68 (1992).
86. Hudspeth WJ, Pribram KH. Stages of brain and cognitive maturation. J Educ Psychol 82:881–884 (1990).
87. Nottelmann ED, Susman EJ, Inoff-Germain G, Cutler GB Jr, Loriaux DL, Chrousos GP. Developmental processes in early adolescence: relationships between adolescent adjustment problems and chronologic age, pubertal stage and puberty-related serum hormone levels. J Pediatr 110:473–480 (1987).
88. Huttenlocher PR. Synaptic density in human frontal cortex-developmental changes and effects of aging. Brain Res 163:195–205 (1979).
89. Chugani HT, Phelps ME Maxxiota JC. Positron emission tomography study of human brain functional development. Ann Neurol 22:487–497 (1987).
90. Bourgeois JP, Goldman-Rakic PS, Rakic P. Synaptogenesis in the prefrontal cortex of rhesus monkeys. Cereb Cortex 4:78–96 (1994).
91. Goldman-Rakic P. Development of cortical circuitry and cognitive function. Child Dev 58:601–622 (1987).
92. Lidow MS, Rakic P. Scheduling of monoaminergic neurotransmitter receptor expression in the primate. Cereb Cortex 2:410–416 (1992).
93. Rosenberg D, Lewis D. Changes in the dopaminergic innervation of monkey prefrontal cortex during late postnatal development: a tyrosine hydroxylase immunohistochemical study. Biol Psychiatr 36:272–277 (1994).
94. Yakovlev PI, Lecours A. The myelogenetic cycles of regional maturation of the brain. In: Regional Development of the Brain in Early Life (Minkowski A, ed). Oxford:Blackwell, 1967.
95. Benes FM. Myelination of cortical-hippocampal relays during late adolescence. Schizophr Bull 15:585–593 (1989).
96. Pujol J, Vendrell P, Junque C, Marti-Vilalta JL, Capdevila A. When does human brain development end? Evidence of corpus callosum growth up to adulthood. Ann Neurol 34:71–75 (1993).

ED_001854_00010735-00007

97. Hudspeth WJ, Pribram KH. Psychophysiological indices of cerebral maturation. Int J Psychophysiol 12:19–29 (1992).
98. Feinberg I, March JD, Fein G, Floyd RC, Walker JM, Price L. Period and amplitude analysis of 0.5-3 c/sec activity in NREM sleep in young adults. Electroencephalogr Clin Neurophysiol 44:202–213 (1978).
99. Buchsbaum MS, Mansour CS, Teng DG, Zia AD, Siegel BV, Rice DM. Adolescent developmental change in topography of EEG amplitude. Schizophr Res 7:101–107 (1992).
100. Jernigan TL, Trauner DA, Hesselink JR, Tallal PA. Maturation of the human cerebrum observed in vivo during adolescence. Brain 114:2037–2049 (1991).
101. Giedd J, Vaituzis A, Hamburger S, Lange N, Rajapakse J, Kaysen D, Vauss Y, Rapoport J. Quantitative MRI of the temporal lobe, amygdala, and hippocampus in normal human development: ages 4–18 years. J Comp Neurol 366:223–230 (1996).
102. Arnold A, Gorski R. Gonadal steroid induction of structural sex differences in the central nervous system. Ann Rev Neurosci 7:413–442 (1984).
103. Toran-Allerand C. Mechanisms of estrogen action during neural development: mediation by interactions with the neurotrophins and their receptors? J Steroid Biochem Mol Biol 56:169–178 (1996).
104. Witelson S, Glezer I, Kigar D. Women have greater density of neurons in posterior temporal cortex. J Neurosci 15:3418-3428 (1995).
105. Bishop K, Wahlsten D. Sex differences in the human corpus callosum: myth or reality? Neurosci Biobehav Rev 21:581–601 (1997).
106. Bear M, Kleinschmidt A, Gu W, Singer W. Disruption of experience-dependent synaptic modifications in striate cortex by infusion of an NMDA receptor antagonist. J Neurosci 10:909–925 (1990).
107. Yen LH, Sibley JT, Constantine-Paton M. Fine-structural alterations and clustering of developing synapses after chronic treatment with low levels of NMDA. J Neurosci 13:4949–4960 (1993).
108. Farber N, Wozniak D, Price M, Labruyere J, Huss H, St. Peter H, Olney J. Age-specific neurotoxicity in the rat associated with NMDA receptor blockade: potential relevance to schizophrenia. Biol Psychiatr 38:788–796 (1995).
109. Parnevales JG, Blue ME. The role of the noradrenergic system on the formation of synapses in the visual cortex of the rat. Brain Res 225:140–144 (1982).
110. Amaral D, Avendano C, Cowan W. The effects of neonatal 6-hydroxydopamine treatment on morphological plasticity in the dentate gyrus of the rat following entorhinal lesions. J Comp Neurol 194:171–191 (1980).
111. Soto-Moyano R, Hernandez A, Perez H, Ruiz S, Galleguillos X, Belmar J. Yohimbine early in life alters functional properties of interhemispheric connections of rat visual cortex. Brain Res Bull 26:259–263 (1991).
112. Soto-Moyano R, Hernandez A, Perez H, Ruiz S, Carreno P, Alarcon S, Belmar J. Clonidine treatment during gestation prevents functional deficits induced by prenatal malnutrition in the rat visual cortex. Int J Neurosci 76:237–248 (1994).
113. Spear L, Brake S. Periadolescence: age-dependent behavioral and psychopharmacological responsivity in the rat. Dev Psychobiol 16:83–109 (1983).
114. Seeman P, Bzowej N, Guan H, Bergeron C, Becker L, Reynolds G, Bird E, Riederer P, Jellinger K, Watanabe S, et al. Human brain dopamine receptors in children and aging adults. Synapse 1:399–404 (1987).
115. Andersen S, Rutstein M, Benzo J, Hostetter J, Teicher M. Sex differences in dopamine receptor overproduction and elimination. Neuroreport 8:1495–1498 (1997).
116. Andersen S, Dumont N, Teicher M. Developmental differences in dopamine synthesis inhibition by ±-7-OH-DPAT. Naunyn-Schmiedeberg's Arch Pharmacol 356:173–181 (1997).
117. Andersen S, Thompson A, Teicher M. D2, but not D1, dopamine receptor overproduction is influenced by gonadal hormones during adolescence. Abstr Soc Neurosci 24:858 (1998).
118. Teicher M, Barber N, Gelbard H, Gallitano A, Campbell A, Marsh E, Baldessarini R. Developmental differences in acute nigrostriatal and mesocorticolimbic system response to haloperidol. Neuropsychopharmacology 9:147–156 (1993).
119. Teicher M, Andersen S, Hostetter JJ. Evidence for dopamine receptor pruning between adolescence and adulthood in striatum but not nucleus accumbens. Brain Res Dev Brain Res 89:167–172 (1995).
120. Seidler F, Levin E, Lappi S, Slotkin T. Fetal nicotine exposure ablates the ability of postnatal nicotine challenge to release norepinephrine from rat brain regions. Brain Res Dev Brain Res 69:288–291 (1992).
121. Swartzwelder H, Wilson W, Tayyeb M. Age-dependent inhibition of long-term potentiation by ethanol in immature versus mature hippocampus. Alcohol Clin Exp Res 19:1480–1485 (1995).
122. Swartzwelder H, Wilson W, Tayyeb M. Differential sensitivity of NMDA receptor-mediated synaptic potentials to ethanol in immature versus mature hippocampus. Alcohol Clin Exp Res 19:320–323 (1995).
123. Zecevic M, Bourgeois J-P, Rakic P. Changes in synaptic density in motor cortex of rhesus monkey during fetal and postnatal life. Dev Brain Res 50:11–32 (1989).
124. Metzger S, Akil M, Herman M, Shannon-Weickert C, Hyde T, Kleinman J. Gene expression of dopamine receptors in the human prefrontal cortex during postnatal development. Abstr Soc Neurosci 24:305 (1998).
125. Meador-Woodruff J, Damask S, Watson SJ. Differential expression of autoreceptors in the ascending dopamine systems of the human brain. Proc Natl Acad Sci USA 91:8297–8301 (1994).
126. Anokhin A, Birbaumer N, Luzenberger W, Nikolaev A, Vogel F. Age increases brain complexity. Electroencephalogr Clin Neurophysiol 99:63–68 (1996).
127. Hill SY, Steinhauer S. Assessment of prepubertal and postpubertal boys and girls at risk for developing alcoholism with P300 from a visual discrimination task. J Stud Alcohol 54:350–358 (1993).
128. Shibasaki H, Miyazaki M. Event-related potential studies in infants and children. J Clin Neurophysiol 9:408–418 (1992).
129. Allison T, Wood C, Goff W. Brain stem auditory, pattern-reversal visual and short latency somatosensory evoked potential latencies in relation to age, sex, brain and body size. Electroencephalogr Clin Neurophysiol 55:619–636 (1983).
130. Evans W, Cui L, Starr A. Olfactory event-related potentials in normal human subjects: effects of age and gender. Electroencephalogr Clin Neurophysiol 95:293–301 (1995).
131. Emmerson-Hannover R, Shearer D, Creel D, Dustman R. Pattern reversal evoked potentials: gender differences and age-related potentials in amplitude and latency. Electroencephalogr Clin Neurophysiol 92:93–111 (1994).
132. Courchesne E. Chronology of postnatal human brain development: event-related potential, positron emission tomography, myelinogenesis and synaptogenesis studies. In: Issues in Event-Related Potential Research: Basic Issues and Applications (Rohrbaugh J, Parasuraman R, Johnson R, eds). New York:Oxford University Press, 1990;210–241.
133. Johnson R, Ross J. Event-related potential indications of altered brain development in Turner Syndrome. In: Atypical Cognitive Deficits in Developmental Disorders: Implications for Brain Function (Broman S, Grafman J, eds). Hillsdale, NJ:Lawrence Erlbaum Associates, 1994;217–242.
134. Kail R. Processing time decreases globally at an exponential rate during childhood and adolescence. J Exp Child Psychol 56:254–265 (1993).
135. Carskadon M, Acebo C, Richardson G, Tate B, Seifer R. An approach to studying circadian rhythms of adolescent humans. J Biol Rhythms 12:278–289 (1997).
136. Feinberg I. Changes in sleep cycle patterns with age. J Psychiatr Res 10:283–306 (1974).
137. Golub M, Takeuchi P, Hoban-Higgins T. Nutrition and circadian activity offset in adolescent rhesus monkeys, In: Adolescent Sleep Patterns: Biological, Social, and Psychological Influences (Carskadon M, ed). New York:Cambridge University Press, in press.
138. Sieck GC, Ramaley JA, Harper RM, Taylor AN. Puberty-related alterations in the organization of sleep-wakefulness states: differences between spontaneous and induced pubertal conditions. Exp Neurol 61:407–420 (1978).
139. Gray LJ, Ostby J, Ferrell J, Rehnberg C, Linder R, Cooper R, Goldman J, Slott V, Laskey J. A dose-response analysis of methoxychlor-induced alterations of reproductive development and function in the rat. Fundam Appl Toxicol 12:92–108 (1989).
140. Chapin R, Harris M, Davis B, Ward S, Wilson R, Mauney M, Lockhart, Smialowicz R, Moser V, Burka L, et al. The effects of perinatal/juvenile methoxychlor exposure on adult rat nervous, immune, and reproductive system function. Fundam Appl Toxicol 40:138–157 (1997).
141. Reel J, Lamb JI, Neal B. Survey and assessment of mammalian estrogen biological assays for hazard characterization. Fundam Appl Toxicol 34:288–305 (1996).
142. Welch R, Levin W, Conney A. Estrogenic action of DDT and its analogs. Toxicol Appl Pharmacol 14:358–364 (1969).
143. Wong K, Klaassen C. Age difference in the susceptibility to cadmium-induced testicular damage in rats. Toxicol Appl Pharmacol 55:456–466 (1980).
144. Lafuente A, Marquez N, Piquero S, Esquifino A. Cadmium affects the episodic luteinizing hormone secretion in male rats: possible age-dependent effects. Toxicol Lett 104:27–33 (1999).
145. Nyberg C, Hiney J, Minks J, Dees L. Ethanol alters *N*-methyl-DL-aspartic acid-induced secretion of luteinizing hormone releasing hormone and the onset of puberty in the female rat. Neuroendocrinology 57:863–868 (1993).
146. Anderson RJ, Willis B, Phillips J, Oswald C, Zaneveld L. Delayed pubertal development of the male reproductive tract associated with chronic ethanol ingestion. Biochem Pharmacol 36:2157–2167 (1987).
147. Little P, Kuhn C, Wilson W, Swartzwelder H. Differential effects of ethanol in adolescent and adult rats. Alcohol Clin Exp Res 20:1346–1351 (1996).
148. Swarzwelder H, Richardson R, Markwise-Foerch B, Wilson W, Little P. Developmental differences in the acquisition of tolerance to ethanol. Alcohol 15:311–314 (1998).
149. Rajachandran L, Spear N, Spear L. Effects of combined administration of the 5-HT3 antagonist MDL 72222 and ethanol on conditioning in the periadolescent and adult rat. Pharmacol Biochem Behav 46:535–542 (1993).
150. Richards G, Terblanche A, Theron A, Opperman L, Crowther G, Myer M, Steenkamp K, Smith F, Dowdeswell R, van der Merwe C. Health effects of passive smoking in adolescent children. S Afr Med J 86:143–147 (1996).
151. Prokhorov A, Emmon K, Pallonen U, Tsoh J. Respiratory response to cigarette smoking among adolescent smokers: a pilot study. Prev Med 25:633–640 (1996).
152. Gold D, Wang X, Wypij D, Speizer F, Ware J, Dockery D. Effects of cigarette smoking on lung function in adolescent boys and girls. N Engl J Med 335:931–937 (1996).
153. U.S. EPA Health Effects Research Laboratory. Neurotoxic Potential of Pesticides: Age-Related Effects of Pesticides Relevant to Youth in Agriculture. Research Triangle Park, NC:U.S. Environmental Protection Agency, 1984.
154. Ronis M, Badger T, Shema S, Roberson P, Templer L, Ringer D, Thomas P. Endocrine mechanisms underlying the growth effects of developmental lead exposure in the rat. J Toxicol Environ Health 22:101–120 (1998).
155. Ronis M, Badger T, Shema S, Roberson P, Shaikh F. Effects on pubertal growth and reproduction in rats exposed to lead perinatally or continuously throughout development. J Toxicol Environ Health 53:327–341 (1998).
156. Hammond P, Minnema D, Shulka R. Lead exposure lowers the set point for food consumption and growth in weanling rats. Toxicol Appl Pharmacol 106:80–87 (1990).
157. Hammond P, Minnema D, Succop P. Reversibility of lead-induced depression of growth. Toxicol Appl Pharmacol 123:9–15 (1993).
158. Hammond P, Succop P. Effects of supplemental nutrition on lead-induced depression of growth and food consumption in weanling rats. Toxicol Appl Pharmacol 131:80–84 (1995).
159. Minnema D, Hammond P. Effect of lead exposure on patterns of food intake in weanling rats. Neurotoxicol Teratol 16:623–629 (1994).

ED_001854_00010735-00008

Personal Protective Equipment Use and Safety Behaviors Among Farm Adolescents: Gender Differences and Predictors of Work Practices

Deborah B. Reed, RN, PhD;[1,2,3] Steven R. Browning, PhD;[1,2,3] Susan C. Westneat, MA;[1,3] and Pamela S. Kidd, PhD[4,5]

ABSTRACT: ***Context:*** *Children on farms perform work that places them at risk for acute and chronic negative health outcomes. Despite strategies for preventing and reducing the risk of disease and injury, children's use of personal protective equipment and safely equipped farm machinery has generally remained unreported.* ***Purpose:*** *This paper reports the use of personal protective equipment, self-protective work behaviors, and selected risk exposures of children aged 14-19, who perform farm work.* ***Methods:*** *Survey results of adolescent high school students (n = 593) enrolled in agriculture class in Kentucky, Iowa, and Mississippi. Students were part of the sample that participated in the Agricultural Disability Awareness and Risk Education Project.* ***Findings:*** *Boys were at a significantly higher risk of exposure compared to girls, and boys engaged more frequently in risky behavior. Hearing and respiratory protection was used minimally and sporadically. Physical symptoms influenced use of hearing and respirator use, as did physician recommendation to use such protection. Of students who operated farm tractors, only half most frequently operated tractors with safety bars and seat belts. Sixty percent of the students reported using equipment with damaged or missing safety shields.* ***Conclusions:*** *In addition to the usual risks of farm work, adolescents may be at even greater risk by not using personal protective equipment or not having access to machinery that is properly equipped for maximum protection. Health care providers should incorporate advice to adolescents and their parents on risk reduction, particularly on the use of personal protective equipment.*

Two million children and youth live or work for hire in US farms and ranches.[1] By the time these children reach their teens, they frequently perform agricultural work unsupervised, with heavy machinery, and in roles that would be prohibited in other industries.[2-4] The morbidity and mortality among children, as a consequence of their work in this industry, have been well documented.[1] Exposures to noise, to organic and inorganic dusts, and to farm equipment pose substantial hazards to children working in agriculture. Despite strategies for preventing and reducing the risk of disease and injury, adolescents' use of personal protective equipment (PPE) and safely equipped farm machinery has generally remained low. Researchers have investigated adults' safety decisions regarding use of tractors equipped with rollover protective structures (ROPS), PPE, and pesticides;[5-7] however, limited attention has focused on adolescents' use of PPE and safety behaviors in agricultural work.

Adolescent farm workers are at risk for fatal and nonfatal farm injuries. Hard et al reported that young agricultural production workers were 3 times more likely to die on the job than their nonagricultural counterparts.[8] In addition to deaths, adolescents experience a high number of the nonfatal injuries of all

[1]College of Nursing, University of Kentucky, Lexington, Ky.
[2]College of Public Health, University of Kentucky, Lexington, Ky.
[3]Southeast Center for Agricultural Health and Injury Prevention, University of Kentucky, Lexington, Ky.
[4]Arizona State University, Tempe, Ariz.
[5]Pamela S. Kidd is deceased.

This work was funded by CDC/NIOSH (R01CCR414307). The opinions expressed here are those of the authors and may not be reflective of CDC/NIOSH. UK IRB # 03-0230-P2B. We acknowledge the competent editorial assistance of Mr. Joe Petrik and Ms. Erin Lee in preparing this article. We also acknowledge the support from Dr. Robert McKnight and Dr. Henry Cole of the Southeast Center for Agricultural Health and Injury Prevention at the University of Kentucky and the teachers and students who participated in the study. For further information, contact: Deborah B. Reed, RN, PhD, College of Nursing, 315 Health Sciences Learning Center, University of Kentucky, Lexington, KY 40536-0232; e-mail dbreed01@uky.edu.

© 2006 National Rural Health Association

ED_001854_00010736-00001

children who work on farms.[1] When adjusted for work exposure time, adolescent injury rates on farms may surpass those of adults.[9] The Federal Code of Regulations includes the Hazardous Occupations Orders for Agriculture that specify 11 domains of work prohibited to children; compared with other industries, these regulations are difficult to enforce and they exempt children who work on their parents' farms.[10] Regulatory statutes or laws regarding agricultural work of persons under age 16 also vary by state.[11] Despite the obvious need for stricter regulation of children's farm work, support for such advances comes slowly; thus, the burden of protecting children continues to rest upon voluntary adoption of safety precautions.

Children learn farm work by modeling their parents and other authority figures. They strive to please adults[2,12,13] and frequently try to perform tasks that exceed their abilities in an effort to please. The focus of farm work is often chore completion, rather than strict adherence to safe behaviors, so adolescents who model adult behavior may adopt unsafe work practices. Children appraise risk in different ways as their cognitive skills develop. Kidd et al held focus groups with farm children to examine the process of learning farm chores and safety rules.[13] Children admitted to taking short cuts even though it meant breaking safety rules. A similar study conducted in Colorado with 36 Future Farmers of America members found that adolescents recognized the importance of safety rules but made conscious decisions to bend or break them based on their perceived risk of injury.[12] Finally, children are dependent upon decisions made by adults with respect to availability of PPE, investment in newer equipment with safety features, and training and supervision in the tasks that they perform.

In addition to acute trauma, children who perform farm work are at risk for more subtle chronic disorders including hearing loss and decrements in respiratory health. Hearing loss for farm resident teens may exceed that of their urban counterparts.[14] Hearing should be protected during many farm chores commonly performed by adolescents, including working in close proximity to tractors and grain dryers and working in swine or poultry confinement buildings. A report of a hearing conservation project for Wisconsin adolescents[15] noted determinants of hearing protection use included male gender, use of lawn mowers, and use of farm tractors. In addition, respiratory protection is indicated in many farm environments to protect the worker from organic materials such as dust and animal dander, as well as chemical irritants and potentially toxic gases from fermenting crops and animal waste.

Self-protective practices used by farm adolescents to prevent hearing loss, respiratory disease, and acute injury from machinery and equipment are examined by gender in this study. Practices include using PPE, operating tractors with roll bars and seat belts, using equipment in good repair, and actively avoiding stepping over a rotating power take-off (PTO) shaft on equipment. Adolescents engaged in selected, high-risk tasks on farms in Kentucky, Iowa, and Mississippi were the population of interest in this investigation. Gender differences in the performance of farm tasks have been recently described in a number of reports, with males more often involved in tasks involving tractors, farm machinery, and cattle.[3,16,17] Since work exposures, farm tasks, hours worked per week on the farm, training, risk perceptions, and susceptibility may vary by gender and age, it is necessary to consider these differences in the analysis of these safety practices. Understanding the patterns of use of such practices may help researchers develop interventions to decrease injury and illness risk in this population.

Methods

This paper is based on the results of a preintervention demographic survey administered to participants at the onset of the Agricultural Disability Awareness and Risk Education project prior to their participation in a safety program.[18] Farm terms were defined before administering the survey to clarify items. If a participant had a reading disability, the teacher or the researcher administering the survey read the questions to the student. Students were encouraged to ask questions to enhance validity of responses.

Data were collected on participant demographics and on 4 specific farm work exposures that were part of the Agricultural Disability Awareness and Risk Education educational curriculum: exposure to excessive noise, exposure to high levels of dust, unsafe tractor driving practices, and exposure to equipment operated by a PTO. Students were queried about work exposure, use of protective equipment, and physical symptoms related to farm work. Students were asked about tractor overturns and injury outcomes. All surveys were reviewed for completeness or signs of blatant disregard. Surveys that included more than 1 page of missing data were eliminated. None of the surveys exhibited signs of disregard.

Data were entered in EpiInfo version 6 (Centers for Disease Control and Prevention, Atlanta) and converted to SAS (SAS Institute Inc, Cary, NC) data sets for the analysis after error checking of variables.[19] Analyses were performed using SAS version 8. Preliminary analyses included computing frequencies and descriptive statistics for all variables. Descriptive analyses were conducted to examine gender differences in farm work exposures, use of PPE, and injury and

ED_001854_00010736-00002

health outcomes. Prevalence estimates for the affirmative responses to questions and the corresponding prevalence odds ratios (OR) and 95% confidence intervals (CI) were calculated, comparing males to females (referent). Maximum likelihood estimates of the ORs were computed using multiple logistic regression to estimate the associations between age, gender, state of residence, symptoms from specific farm work exposures, and physician recommendations on the use of respirators and hearing protection.

Sample. A subset of the 1,138 high school agriculture students who participated in the research project between 1997 and 2000 was used in the analysis.[18] The project took place in 21 high schools located in Kentucky, Iowa, and Mississippi and focused on 9th- and 10th-grade students enrolled in agriculture classes. States were selected because of previous cooperative working relationships with the researchers, cultural diversity seen across the region, and differences in agricultural production and commodities. This paper reports the results from survey data collected from the 593 students who reported participating in farm work at time of data collection. Passive consent was obtained from parents of the students after sending letters to the parents that explained the study. Only 10 students elected not to participate in the study.

Results

Baseline Characteristics. Demographic characteristics of the 593 children are given in Table 1. The mean age was 15.4 years (SD = 2.0 years). The majority (75%) were in the 9th or 10th grade. The children had a mean of 12 years of farm residence and 7.6 years of performing farm work. No differences were seen by gender for these variables. Males aged 14-15 years represented 46% of the sample, and 62% of the sample was composed of children from Kentucky. Most of the children (71%) who indicated that they currently worked on farms were living on a farm; consequently, 29% of those surveyed who were doing farm work at the time of the survey either did not live on the farm or did not indicate their place of residence. The majority of the children in the sample were white.

Gender-Specific Prevalence Analysis. Table 2 illustrates the exposure of the sample to risky farm work and the subsequent self-reported protective behaviors. Although a high prevalence of exposure to dusty farm jobs was reported for both males and females (91.4% for both), boys were at a significantly higher risk of exposure (OR = 2.72, 95% CI: 1.49-4.97) than girls. Respirators were used by slightly less than 1 in 5 children, and high-efficiency particulate air filter respirators were used by just 11.3%. Overall, boys were twice as likely to report using high-efficiency particulate air filter respirators when doing farm work than were girls. Over one fourth reported difficulty breathing after doing dusty farm work, with girls indicating a slight, but not statistically significant, elevated risk of breathing problems. Work in grain storage, hay, and in poultry facilities was cited as problematic for dust exposure.

The prevalence of exposure to noisy work was comparable with exposure to dusty work, with a slightly higher prevalence for males (94%) than for females (84%). Males were more likely to have experienced ringing in the ears (OR = 1.39, 95% CI: 0.90-2.15) than females, but this difference was not significant. Hearing protection was used by slightly more than one fourth of the children. Use of hearing protection was significantly more prevalent than use of

Table 1. Demographic Characteristics of Children (Aged 14-19 Years) Currently Living in a Farm in Kentucky, Iowa, and Mississippi (N = 593)

Characteristic	Children in Sample $N_{(s)}$*	Percent
Gender/age		
Male		
14-15 y	272	45.9
16-17 y	149	25.1
18-19 y	30	5.1
Missing	2	0.3
Female		
14-15 y	81	13.7
16-17 y	51	8.6
18-19 y	8	1.3
Missing	—	—
Race		
White	511	86.2
Black and other	5	0.8
Missing	77	13.0
State		
Kentucky	368	62.1
Iowa	198	33.4
Mississippi	27	4.6
Year in high school		
Freshman	288	48.6
Sophomore	154	26.0
Junior	78	13.2
Senior	71	12.0
Missing	2	0.3
Live on farm now		
Yes	421	71.0
No	75	12.6
Missing	97	16.4

*$N_{(s)}$ is the number in the sample for the variable reported.

ED_001854_00010736-00003

Table 2. Gender Differences in Exposure to Respiratory, Hearing, Tractor, and PTO Hazards for Children Who Currently Work on Farms*

Exposure Characteristic	$N_{(s)}$	Number of "Yes" Responses	Percent "Yes" Responses	OR, 95% CI
Respiratory				
Perform dusty jobs†				
Male	434	406	93.6	2.72, 1.49-4.97
Female	133	112	84.2	
Use respirator on farm				
Male	404	84	20.8	1.07, 0.62-1.88
Female	112	22	19.6	
Use high-efficiency particulate air filter doing farm work†				
Male	401	55	13.7	2.29, 1.00-6.15
Female	108	7	6.5	
Have difficulty breathing after dusty work				
Male	402	115	28.6	0.80, 0.50-1.29
Female	111	37	33.3	
Hearing				
Perform farm work with noisy equipment				
Male	421	379	90.0	1.38, 0.76-2.48
Female	136	118	86.8	
Use hearing protection while farming				
Male	379	110	29.0	1.01, 0.63-1.64
Female	118	34	28.8	
Have experienced ringing in the ears				
Male	378	232	61.4	1.39, 0.90-2.15
Female	118	63	53.4	
Tractor				
Ever drive a tractor with ROPS†				
Male	425	311	73.2	2.48, 1.65-3.73
Female	128	67	52.3	
Drive tractor with ROPS and seat belt				
Male	310	230	74.2	0.76, 0.40-1.44
Female	67	53	79.1	
Tractor used most has ROPS and seat belt				
Male	314	172	54.8	1.05, 0.63-1.76
Female	71	38	53.5	
Ever overturned tractor†				
Male	399	29	7.3	8.15, 1.10-60.55
Female	105	1	1.0	
Ever injured in a tractor overturn				
Male	423	12	2.8	—
Female	129	0	—	
PTO equipment				
Perform farm work using PTO equipment†				
Male	427	390	91.3	4.50, 2.74-7.40
Female	137	96	70.1	
Have ever stepped over rotating PTO†				
Male	389	168	43.2	2.52, 1.46-4.38
Female	95	22	23.2	
Used equipment with missing/damaged PTO shield†				
Male	390	253	64.9	2.89, 1.78-4.72
Female	95	37	39.0	
Ever injured from stepping over PTO shaft				
Male	390	8	2.0	—
Female	96	0	0	—

*Overall analysis based on responses from 453 male and 140 female children who currently work on farms (n = 593). $N_{(s)}$ is the number in the sample for the variable reported. Missing values constituted less than 8% of responses for any question. Analysis for the respiratory, hearing, and PTO exposure questions were restricted to the subset of responses that answered affirmatively to performing dusty jobs, performing farm work with noisy equipment, and performing farm work with PTO equipment, respectively, following the initial question in the category. The question concerning driving tractors with ROPS and seat belts and the question regarding whether the tractor used most often has an ROPS and seat belts were restricted to children who responded that they had ever driven a tractor. Ever injured in a tractor overturn is based on the total number of children reporting ever having driven a tractor.
†Statistically significant result at the $P < .05$ level.

ED_001854_00010736-00004

respirators among children in the sample. Males reported using hearing protection most often while participating in shooting sports, including hunting on farm property. Females reported highest use while feeding pigs in confinement buildings.

Only half of the children who drove tractors on the farm most often used a tractor with an ROPS and a seat belt. Tractor-related "near misses" and injuries were almost exclusively reported by males, with 7% (n = 29) of the boys who drove tractors indicating that they had overturned the tractor. Of those who had overturned a tractor, 41% indicated they were injured in the incident. Overall, we estimate that about 3% of males aged 14-19 who drive tractors on the farm are injured in a tractor overturn. Over a third (39%) reported ever stepping over a rotating PTO shaft; however, 59.8% reported using equipment with missing or damaged shields. Boys were 4.5 times more likely to engage in farm work that included using PTO equipment (OR = 4.50, 95% CI: 2.74-7.40) and were more than 2.5 times as likely to step over a rotating PTO shaft (OR = 2.52, 95% CI: 1.46-4.38) than were girls. Eight children reported being injured by a PTO shaft, and 2 of these were hospitalized for their injuries.

Frequency of Use Analysis. We examined frequency of use patterns for the use of respirators, hearing protection, and seat belts on ROPS-equipped tractors by gender. These data revealed that when queried about use of a given type of PPE in the last 10 times it should have been used, the self-reported frequency of use tended to be very low (1-3 times) for respirators and hearing protection. Excluding those who reported never using respirators or hearing protection, the median frequency for either type of protection was 4 times in the last 10 times. There were no significant differences by gender for either type of protection.

Across all frequency categories for use of seat belts on ROPS-equipped tractors, girls were more likely than boys to wear seat belts when operating the tractor ($P = .0002$). Girls reported a median seat belt use of 6 out of every 10 times they drove an ROPS-equipped tractor, while the median reported seat belt use for boys was 4 out of every 10 times.

Logistic Regression Analysis: Predictors of Use of PPE. Logistic regression models were used to examine gender differences in the use of 2 types of PPE (ie, respirators and hearing protection, considered separately as dependent variables) while controlling for state of residence, child's age, symptoms related to breathing difficulties, and noise exposure for each outcome, and physician-recommended use of the specific protective equipment.

Results from the logistic regression for use of respirators indicate that children from Iowa were more likely to wear respiratory protection ($OR_{adj} = 8.05$, 95% CI: 4.82-13.46) compared to children from Mississippi ($OR_{adj} = 2.60$, 95% CI: 0.81-8.37) or Kentucky (referent). Adolescents who reported breathing difficulties after exposure to dusty farm work were 1.5 times more likely to use a respirator than those not reporting breathing difficulties. This suggests that prevalence of breathing difficulties among children influenced their use of respirators. After controlling for these variables, the model indicated that males were slightly more likely to use a respirator than females ($OR_{adj} = 1.47$, 95% CI: 0.82-2.63) and that physician recommendations may have a modest influence on respirator use among children ($OR_{adj} = 1.50$, 95% CI: 0.81-2.76), but neither finding was statistically significant.

Results of the logistic regression for use of hearing protection indicated that boys were slightly more inclined to use hearing protection than girls ($OR_{adj} = 1.20$, 95% CI: 0.77-1.87), and those students reporting ringing in the ears were more likely to report using hearing protection than those who did not report ringing ($OR_{adj} = 1.18$, 95% CI: 0.79-1.74), but neither finding was statistically significant. Those children who reported that a doctor had recommended that hearing protection be used were 2.4 times more likely to use hearing protection ($OR_{adj} = 2.42$, 95% CI:1.27-4.61), while children from Iowa were about twice as likely to use hearing protection ($OR_{adj} = 1.93$, 95% CI:1.30-2.86) than children in Mississippi or Kentucky (referent).

Discussion

The results of the study confirm that a high proportion of boys and girls working on farms are exposed to dusty and noisy work environments. Among those children who have ever used a respirator, the majority reported infrequent use when undertaking dusty farm jobs but with no significant difference in the frequency of use of respirators by gender. Boys, however, were more likely to use a high-efficiency particulate air filter while doing farm work, which may be a function of the tasks performed and familiarity with the equipment. Children were more likely to use hearing protection than respirators, even though the prevalence of exposure to noisy jobs was comparable to that of the dusty ones. The low overall prevalence of PPE use in our study parallels the use of PPE among Midwestern adult farmers, although adolescents in Iowa were more likely than youth in Kentucky or Mississippi to use PPE.[6] This regional variation could be due to cultural attitudes toward safety devices, more extensive farm safety education, or different agricultural practices.

ED_001854_00010736-00005

Symptoms related to dust or noise exposures appear to have influenced children's use of respirators and hearing protection. Respirator use among children with breathing difficulties and use of hearing protection among children reporting ringing in the ears support the finding of Kidd et al that negative events influence behavior.[13] Although a history of respiratory and hearing problems in child farm workers may have prompted their parents to encourage PPE use for their children, the adolescents in this study frequently worked unsupervised and independently and wore the protective devices when exposure to dust and noise was excessive. It may be that the use of these protective devices was less frequent when the youth did not perceive a high level of risk or if the youth had not experienced a health problem due to the exposure.

There has been no examination of the efficacy of providing agricultural health advice by health care providers. In this study, the advice of a health provider to use respiratory and hearing protection seemed to influence the use of these devices. Perhaps their symptoms prompted them to seek medical attention, so these adolescents took action to protect their health when advised to do so by their physicians. This possible effect from physician recommendation was mitigated by the infrequent use of the equipment.

The survey did not query about the fit of the PPE device or if the student had been instructed on its use. These issues are important when determining the use and effectiveness of PPE and should be explored more fully. Only a few reports have focused on PPE fit and availability for women.[20-22] These reports noted that very little has been done to ensure adequate access to or design of PPE to accommodate female workers in any industry.

In addition to the PPE discussed in this report, the use of other protective equipment, shoes, and clothing should be examined. The guidelines for determining children's and adolescents' farm work assignments and use of PPE provided by the North American Guidelines for Children's' Agricultural Tasks (www.nagcat.org) could also be offered by health providers when counseling parents and youth.

The literature shows that access to farm equipment and safety information varies by gender, with females historically not having equal access to farm safety information.[23,24] In our analyses, except for seat belt use on tractors, girls were less likely to use PPE. Girls may be more familiar with seat belts than with other types of PPE and thus make the translation of seat belt use in a vehicle to that on a tractor. Tasks requiring respiratory or hearing protection would not have this ready translation. Perhaps females have less exposure to the need for PPE, or perhaps they do not have equal access to PPE. Disparities in PPE use may also result from the fit of the PPE itself.[20-22] While seat belts are adjustable, respiratory and hearing protection is generally designed to fit adults. The PPE may not properly fit female adolescents or may be uncomfortable.

Despite years of educational efforts to promote use of roll bars on tractors and efforts to inform about the high risk of fatal outcomes from tractor overturns, only half of the participants in this study who operated tractors reported that the tractor they drive most often is equipped with a roll bar and seat belt. These easily adopted safety measures have been calculated to reduce fatalities and injuries from tractor overturns by as much as 98%.[25] Buckling the seat belt on a vehicle so equipped should be second nature; however, very few of the participants routinely used a seat belt when driving a tractor. Often, the tractor driven most often by the teens in the study was not even equipped with a seat belt.

This study found that boys who drive tractors on the farm were 8 times more likely to overturn them than girls. It is documented that males begin tractor driving at younger ages than females and have more tractor driving time;[26] thus, it would be expected that male overturn rates would surpass corresponding female rates. This risk should be countered with protective strategies beyond tractor driving instruction. Operation of tractors not equipped with ROPS or seat belts should be prohibited by law among all youth regardless of family status. Similar legislation could be effective in reducing PTO-induced injuries.

Limitations. The survey used a cross-sectional, self-report design. The use of the prevalence OR for the estimation of risk in this study may lead to overestimates of the risk for outcomes that are more prevalent than 10% in the population.[27-29] However, the relative ranking of risk factors on the basis of adjusted ORs from the logistic regression analysis in this study still yields appropriate inferences from the data and is a commonly used approach for the adjustment of multiple confounders in cross-sectional studies.[30,31] Work exposures may have been underreported or overreported because of the seasonality of agricultural production and the time limitations of farm work imposed by the child's attendance at school, with recall potentially biased toward more recent work. In addition, much of the data were collected during late fall and winter, a time when farm work is minimal, which could result in underreporting. The sample was located primarily in Kentucky, which could bias results toward work performed on smaller farms, where work and PPE use may differ from other regions where farms tend to be larger.

The schools were not randomly selected; thus, the external validity of the findings may not be generalizable

ED_001854_00010736-00006

to the entire United States. However, the sample does represent a diversity of agricultural commodities and geographic locations, which tempers bias. The work practices examined focused on common agricultural tasks known to be high-risk activities in any farm setting.

While there are evident limitations to this cross-sectional study, it does provide evidence to support the need for randomized community trials of interventions to encourage the use of PPE among farm children.

Conclusion

Children and adolescents, especially adolescents aged 15-19, continue to be at high risk for acute injury and cumulative trauma when performing farm work. Teens in this study were able to identify hazardous conditions; yet, few took precautions that could prevent personal injury. Simple and inexpensive PPE is available, but use of these devices typically occurs among a small proportion of farm children and is inconsistent. When confronted by symptoms that might be averted by PPE, youths were more inclined to wear the devices. Health care providers may be instrumental in increasing PPE use and improving other protective strategies. Further work with health professionals that promotes the advantages of PPE may be beneficial.

References

1. Myers JR, Hendricks KJ. *Injuries Among Youth on Farms in the United States, 1998*. Cincinnati, Ohio: NIOSH; 2001. DHHS Publication No. 2001-154.
2. Lee B, Marlenga B., eds. *Professional Resource Manual: North American Guidelines for Children's Agricultural Tasks*. Marshfield, Wis: Marshfield Clinic; 1999.
3. Marlenga B, Pickett W, Berg RL. Agricultural work activities reported for children and youth on 498 North American farms. *J Agric Saf Health*. 2001;7:241-252.
4. US General Accounting Office. *Child Labor in Agriculture: Characteristics and Legality of Work*. Washington, DC: US General Accounting Office; 1998. Publication No. HSHS-98-112R.
5. Cole HP, Westneat SC, Browning SR, Piercy LR, Struttmann T. Sex differences in principal farm operators' tractor driving safety beliefs and behaviors. *J Am Med Womens Assoc*. 2000;55(2):93-95.
6. Carpenter WS, Lee BC, Gunderson PD, Stueland DT. Assessment of personal protective equipment use among Midwestern farmers. *Am J Ind Med*. 2001;42:236-247.
7. Meeker BJ, Carruth A, Holland CB. Health hazards and preventive measures of farm women, emerging issues. *AAOHN J*. 2002;50:307-314.
8. Hard D, Myers J, Snyder K, et al. Young workers at risk when working in agricultural production. *Am J Ind Med*. 1999; 36(suppl 1):31-33.
9. Castillo DN, Landen DD, Layne LA. Occupational injury deaths of 16- and 17-year-olds in the United States. *Am J Public Health*. 1994;84:646-649.
10. Murphy DJ. Strategy: regulations to require behavior change. In: *Safety and Health for Production Agriculture*. St Joseph, Mich: American Society of Agricultural Engineers; 1992:155-177.
11. US Department of Labor. State child labor laws applicable to agricultural employment, January 1, 2005. Available at: http://www.dol.gov/esa/programs/whd/state/agriemp2.htm. Accessed June 1, 2005.
12. Darragh AR, Stallones L, Sample PL, Sweitzer K. Perceptions of farm hazards and personal safety behavior among adolescent farmers. *J Agric Saf Health*. 1998;1(special issue):159-169.
13. Kidd P, Townley K, Cole H, McKnight R, Piercy L. The process of chore teaching: implications for farm youth injury. *Fam Community Health*. 1997;19(4):78-89.
14. Broste SK, Hansen DA, Strand RL, Stueland DT. Hearing loss among high school farm students. *Am J Public Health*. 1989;79:619-622.
15. Knobloch MJ, Broste SK. A hearing conservation program for Wisconsin youth working in agriculture. *J Sch Health*. 1998;68:313-318.
16. Hawk C, Donham KJ, Gay J. Pediatric exposure to agricultural machinery: implications for primary prevention. *J Agromedicine*. 1994;1(1):57-74.
17. Lee BC, Jenkins LS, Westaby JD. Factors influencing exposure of children to major hazards on family farms. *J Rural Health*. 1997;13:206-215.
18. Reed DB, Kidd PS, Westneat SC, Rayens MK. Agricultural Disability Awareness and Risk Education (AgDARE) for high school students. *Inj Prev*. 2001;7(suppl 1):i59-i63.
19. *Epi Info™ [Computer Program]. Version 6.04a*. Atlanta, Ga: Centers for Disease Control and Prevention; 1996.
20. Industrial Accident Prevention Association. Personal protective equipment for women: addressing the need. IAPA Web site. 2002. http://www.iapa.ca/pdf/FreeDownloads10-persprot.pdf. Accessed November 22, 2004.
21. Schuster MP. The physical and psychological stresses of women in firefighting. *Work*. 2000;15(1):77-82.
22. Tapp L. Making manufacturing a safe work environment for women workers. *Occupational Hazards* [serial online]. 2003;65(10):26. Available at: http://www.occupationalhazards.com/articles/index.php?id=10725. Accessed November 22, 2004.
23. Leckie GJ. 'They never trusted me to drive': farm girls and the gender relations of agricultural information transfer. *Gend Place Cult*. 1996;3:309-326.
24. Schulman MD, Evensen CT, Runyan CW, Cohen LR, Dunn KA. Farm work is dangerous for teens: agricultural hazards and injuries among North Carolina teens. *J Rural Health*. 1997;13:295-305.
25. Cole HP. Farmers' perceptions of ROPS and tractor safety: studies, stories, and statistics. Paper presented at: the NIOSH Tractor-related Death and Injury Workshop; February, 2003; Pittsburgh, Pa.
26. Browning SR, Westneat SC, Szeluga R. Tractor driving among Kentucky farm youth: results from the farm family health and hazard surveillance project. *J Agric Saf Health*. 2001;7(3):155-167.
27. Thompson ML, Myers JE, Kriebel D. Prevalence odds ratio or prevalence ratio in the analysis of cross sectional data: what is to be done? *Occup Environ Med*. 1998;55:272-277.
28. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA*. 1998;280:1690-1691.
29. Behrens T, Taeger D, Wellmann J, Keil U. Different methods to calculate effect estimates in cross-sectional studies. A comparison between prevalence odds ratio and prevalence ratio. *Methods Inf Med*. 2004;43:505-509.
30. Kleinbaum D, Kupper L, Morgenstern H. *Epidemiologic Research: Principles and Quantitative Methods*. New York, NY: Van Nostrand Reinhold Company; 1982.
31. Hosmer D, Lemeshow S. *Applied Logistic Regression*. New York, NY: John Wiley and Sons; 1989.

ED_001854_00010736-00007

Critical Periods of Vulnerability for the Developing Nervous System: Evidence from Humans and Animal Models

Deborah Rice[1] and Stan Barone Jr.[2]

[1]National Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, D.C., USA; [2]Cellular and Molecular Toxicology Branch, National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA

Vulnerable periods during the development of the nervous system are sensitive to environmental insults because they are dependent on the temporal and regional emergence of critical developmental processes (i.e., proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis). Evidence from numerous sources demonstrates that neural development extends from the embryonic period through adolescence. In general, the sequence of events is comparable among species, although the time scales are considerably different. Developmental exposure of animals or humans to numerous agents (e.g., X-ray irradiation, methylazoxymethanol, ethanol, lead, methyl mercury, or chlorpyrifos) demonstrates that interference with one or more of these developmental processes can lead to developmental neurotoxicity. Different behavioral domains (e.g., sensory, motor, and various cognitive functions) are subserved by different brain areas. Although there are important differences between the rodent and human brain, analogous structures can be identified. Moreover, the ontogeny of specific behaviors can be used to draw inferences regarding the maturation of specific brain structures or neural circuits in rodents and primates, including humans. Furthermore, various clinical disorders in humans (e.g., schizophrenia, dyslexia, epilepsy, and autism) may also be the result of interference with normal ontogeny of developmental processes in the nervous system. Of critical concern is the possibility that developmental exposure to neurotoxicants may result in an acceleration of age-related decline in function. This concern is compounded by the fact that developmental neurotoxicity that results in small effects can have a profound societal impact when amortized across the entire population and across the life span of humans. *Key words*: abnormal neurological development, apoptosis, behavioral testing methodology, delayed neurotoxicity, differentiation, migration, myelination, neurobiological substrates of function, neuronal plasticity, neurotrophic factor, primate, rodent. — *Environ Health Perspect* 108(suppl 3):511–533 (2000).
http://ehpnet1.niehs.nih.gov/docs/2000/suppl-3/511-533rice/abstract.html

The vulnerability of the developing brain is dependent on two main exposure issues. The first factor relates to whether an agent or its active metabolite(s) reaches the developing nervous system, and the second factor relates to the period of exposure. Exposure to environmental toxicants coincident with the ontogeny of developmental processes is more likely to cause adverse effects if they interfere with the cascade of these developmental processes. In general, if exposure occurs before or after an organ develops, it is less vulnerable to perturbation than if exposure occurs during development of that organ.

It is critical for the risk assessment of environmental chemicals that we have a good understanding of the time lines of normal neural development in humans and other species used in toxicological testing. This understanding should include both pharmacokinetic and pharmacodynamic factors that may differ across species. Both species- and age-related differences in pharmacokinetic parameters are out of the scope of this review paper, but other papers have attempted to describe these parameters in a limited way with pesticides (*1–5*), metals (*6–10*), and a solvent (*11*).

There is general recognition that the developing nervous system is qualitatively different from the adult nervous system. The normal ontogeny of neural development in rodents is different from humans because rodents have considerable postnatal development and humans have considerably more prenatal maturation of their nervous systems. These differences may be confounded with differences in the route of exposure during critical periods of nervous system development and thus differences in vulnerability between developing animals and humans (e.g., lactational transfer during the first postnatal week in rodents and transplacental transfer during the third trimester in humans).

Key aims of this article are to characterize the profiles of developmental processes, describe similarities and differences in windows of vulnerability between rodents and humans, and describe similarities and differences in effects after perturbations of developmental processes in humans and animal models, including rodents and monkeys. The brain areas subserving various behavioral functions are described for human infants and the ontogeny of these specific structures is discussed in the context of the effects of lesions in nonhuman primates with altered performance on these tasks. This will further our understanding of developmental neurotoxicology, improve our ability to predict adverse outcomes in animals, and assist in the extrapolation of these adverse outcomes to risks to human health.

Development of the Brain *in Utero*

The cell precursors of the brain and spinal cord, which compose the central nervous system (CNS), begin to develop early in embryogenesis through the process called neurulation. The notochord, which is a cellular rod that defines the primitive axis of the embryo, will be incorporated into the vertebral system. The notochord induces the overlying ectodermal tissue to form the neural plate at approximately 2 weeks of gestation in humans. This overlying ectodermal tissue gives rise to the CNS. In humans on approximately gestational day (GD) 18, the neural plate invaginates along its central axis to form the neural groove with neural folds on each side. By the end of the third week of gestation in humans, the neural folds have begun to move together and fuse, forming the neural tube near the anterior end of the notochord; this fusion progresses both cranially and caudally in a zipperlike manner. The neural tube then separates from the overlying ectoderm, which becomes a contiguous surface over the back of the embryo and differentiates into the epidermis of the skin. As the neural tube forms, a population of cells separates from the

This article is based on a presentation at the Workshop to Identify Critical Windows of Exposure for Children's Health held 14–16 September 1999 in Richmond, Virginia.

Address correspondence to S. Barone Jr., Cellular and Molecular Toxicology Branch, Neurotoxicology Division, Mail Drop 74-B, National Health and Environmental Effects Research Laboratory (NHEERL), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711 USA. Telephone: (919) 541-3916. Fax: (919) 541-4849. E-mail: barone.stan@epa.gov

We thank K. Tarpley for photographic assistance and H.A. Tilson, S. McMaster, L. White, and C. Kimmel for editorial comments.

This manuscript was reviewed and approved for publication by the NHEERL, U.S. Environmental Protection Agency. Mention of trade names or commercial products does not constitute endorsement or recommendation for use. The opinions expressed by the authors are not to be misconstrued as policy of the U.S. EPA.

Received 10 January 2000; accepted 17 April 2000.

ED_001854_00010737-00001

surface ectoderm at the apex of the neural folds to form the neural crest, which will give rise to the sensory ganglia of spinal and cranial nerves, Schwann cells (the cells covering peripheral nerves), the meningeal covering of the brain and spinal cord, and some skeletal and muscle components of the head, among other structures. The neural tube begins to close in the area of the hindbrain above the origin of the notochord and proceeds anteriorly and posteriorly, creating a caudal-to-rostral gradient in development of the brain. Neural tube formation is complete at approximately GD 10.5–11 in rats and from GD 26 to 28 in humans; the anterior neuropore closes first (rats GD 10.5, humans GD 24–26) and the posterior neuropore closes later (rats GD 11.3, humans GD 25–28) [reviewed by DeSesso (*12*)].

Interruption of neural development during this early period can result in severe abnormalities of the brain and spinal cord. Spina bifida (divided spine) results from defective induction of mesoderm around the notochord that forms the osseous bone of the spine. There are several types of spina bifida, which range from anomalies in the vertebrae of no significance to severe defects in the spinal cord or brain. Extreme cases of spina bifida (i.e., anencephaly) lead to failure in the closure of the neural tube and severe defects in the spinal cord or brain. For example, failure of neural tube closure results in extroversion of the neural tissue, which then degenerates as in anencephaly, wherein the brain is represented by a mass of degenerated neural tissue exposed on the surface of the head. It has recently been established that an increased intake of folic acid during early gestation or prenatally decreases the prevalence of neural tube defects in offspring (*13*). Increased risk for spina bifida may depend on the mother and/or fetus being homozygous for specific forms of enzymes involved in folate metabolism (*14*).

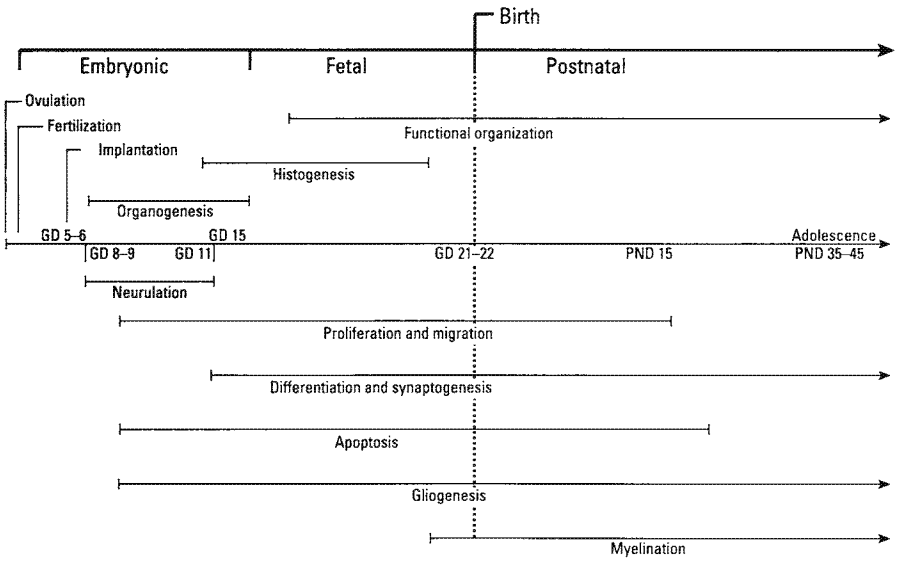


Figure 1. Timelines of developmental processes in the nervous system of rats compared to timing of fertilization, organogenesis, and histogenesis. Modified from Vorhees (*15*) and reprinted with permission of Plenum Press.

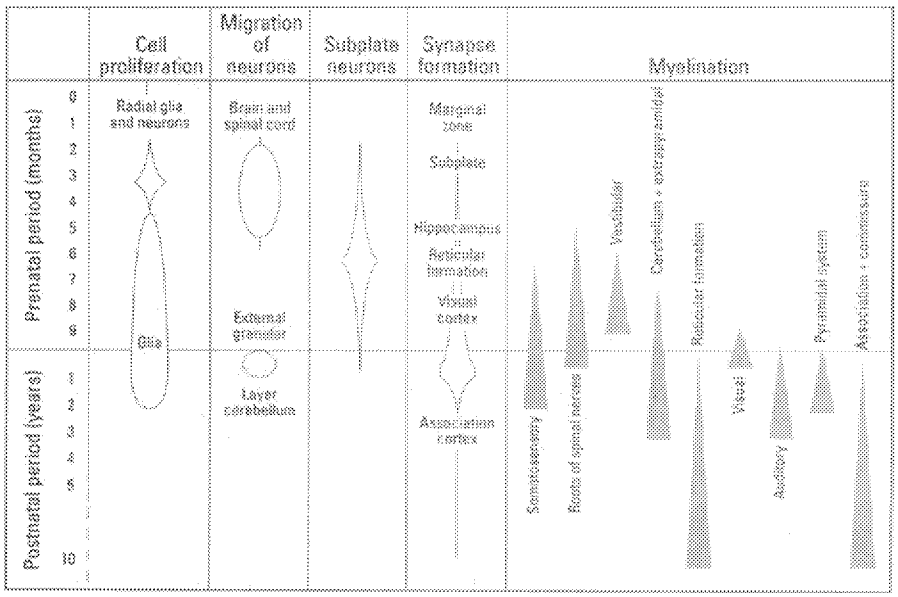


Figure 2. Comparison of timelines for developmental processes in humans. The prenatal period is scaled in months and the postnatal development is scaled in years. Adapted from Herschkowitz et al. (*16*) and reprinted with permission of Hippokrates Verlag GmbH.

Beginning early in the second week of gestation in rodents (GD 7 in mouse, GD 9.5 in rats) and the first month of gestation in humans, specific areas of the CNS begin to form with the neurogenesis and migration of cells in the forebrain, midbrain, and hindbrain. There follows a sequence of developmental processes including proliferation, migration, differentiation, synaptogenesis, apoptosis, and myelination [Figures 1 (*15*) and 2 (*16*)].

Alterations in these processes can result in severe congenital abnormalities of the nervous system of humans, with a frequency of 0.74–1.89 cases per 1,000 births according to a recent survey (*17*). These overt abnormalities include conditions that produce extremely severe functional deficits and which may be incompatible with life, including anencephaly, hydrocephaly, and herniation of the spinal cord. Significant risk factors associated with these conditions include parental age, toxemia in the mother, threatened interruption of the pregnancy, and prematurity or intrauterine hypotrophy. A literature survey of > 70 studies from various countries (*18*) found that the incidence of mental retardation is approximately 4 per 1,000 births, although, as stated by the authors, the true prevalence is difficult to determine.

Regional Development of the Rodent and Primate Brain

In general, regional development of the rodent brain proceeds on a timeline of days versus weeks to months in humans, although gross regional development of the brains of rodents and humans is similar. In the case of specific structures, however, there may be differences in the relative mass and/or volume of a specific structure between species. Examples include the relatively larger mass of the neocortex and visual system in humans versus that of rats. Conversely, the relative mass of the olfactory system is larger in rodents than in humans. The gradients of maturation of developing regions of the nervous system in rats and humans follow the same general sequence, with more caudal regions like the hindbrain {metencephalon and myelencephalon [Figure 3 (*19*)]} developing earlier than the more rostral areas like the forebrain (telencephalon and diencephalon) and with the more medial

ED_001854_00010737-00002

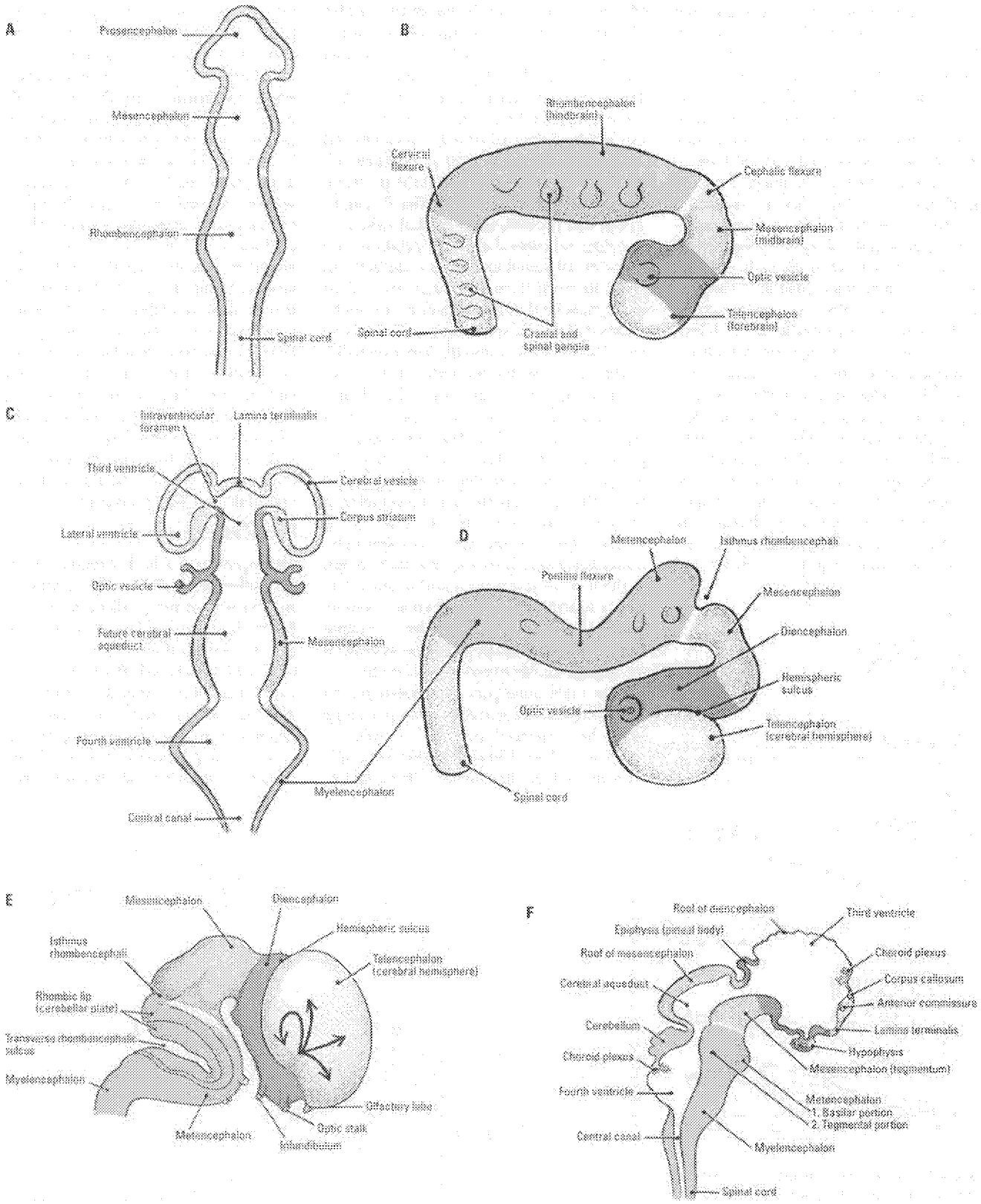


Figure 3. Development of the brain vesicles and subsequent brain divisions of the mammalian brain. (*A*) and (B) The development of the three primary brain vesicles on GD 10.5 in rats and GD 26 ± 1 in humans. The corresponding shading between panels illustrates the earlier origins of different regions from the three original brain vesicles with a horizontal and lateral view, respectively. (*C*) and (*D*) The more mature brain with five brain vesicles: the horizontal and lateral views correspond to GD 11.5 in rats and GD 33 ± 1 in humans. (*E*) The lateral view shows the migratory paths from the more central ventricular zone and gradients maturation of the neocortex (see arrows). (*F*) The midsagittal view of the brain and spinal cord, with the major divisions delineated and the continuity of the ventricles noted; the formation of the choroid plexus corresponds to GD 13.5 in rats and GD 48–51 in humans. Adapted from Carpenter and Sutin (*19*) and reprinted with permission of Williams and Wilkins.

ED_001854_00010737-00003

aspects of these structures maturing earlier than more lateral aspects. The pons, medulla, and cerebellum make up the hindbrain. The pons and medulla include brainstem motor and sensory nuclei that mature relatively early and, for the most part, coincident with craniofacial development during the embryonic period of both rats (GD 10–16) and humans (3–7.5 weeks of gestation). Although the above generalizations are useful, there are exceptions to the rostral-to-caudal gradients. One exception is apparent in the delayed development of the cerebellum relative to the early development of other hindbrain structures. The cerebellum is a caudal structure that arises from the dorsal lips of the hindbrain and develops largely later in brain development in both rats and humans than the other cranial nerve nuclei of the hindbrain. The midbrain or mesencephalon includes dorsally the tectum and ventrally the tegmentum. The tectum includes the superior and inferior colliculus, which proliferate and differentiate during the fetal and embryonic periods in rats and humans, respectively. The tectum continues to develop into the postnatal period with increased synaptogenesis to and from their principal efferent and afferent structures. The diencephalon, which includes the hypothalamic and thalamic nuclei, develops during the late embryonic and early fetal periods in both rats and humans. The forebrain cortical structures of the neocortex and hippocampal formation develop primarily during the fetal period of both rats and humans, with some proliferation of glia and microneurons continuing into the postnatal period. Differentiation and synaptogenesis within and between these cortical structures and their subcortical afferents continue into the postnatal period in both rats and humans. A significant difference between the rodent and human (and other primate) brains can be observed in the size and contour of the neocortex. Rodents have a smooth (lissencephalic) cerebral cortex with a relatively small neocortex. Humans, on the other hand, have brains with a highly convoluted surface (gyrencephalic brain) resulting from the enormous phylogenetic expansion of the neocortex. The ontogeny of specific regions of the brain incorporate the timely progression and completion of these developmental processes. This sequence for a specific region may generalize readily between rodents and humans; however, at the level of integration and connectivity among structures, with the exception of sensory systems, it is often only speculative to extrapolate results from animals to humans because of the limited number of comparative studies.

The brain undergoes tremendous growth beginning early in gestation and continuing into the postnatal period. In rodents, regional and total brain weights are crude estimates of brain development that continue to increase during the postnatal period [Figure 4 (*20*)]. In humans, gross measures of brain growth increase for at least 2–3 years after birth. The growth rate of the brain as a whole, as measured by change in volume, peaks approximately 1.1 years after conception or approximately 4 months after birth (Figure 5). The growth rate of the human diencephalon peaks about the time of birth, whereas the peak rate of growth of the cerebellum is approximately 1.3 years after conception (i.e., 7 months of age) (*21*). It is important to remember that changes in volume represent only crude measures of brain development. In addition, it is noteworthy to emphasize that birth does not represent a divide signifying an absolute change in brain development or the end of any developmental processes. Thus, various parts of the brain develop at different times and have different windows of vulnerability, both prenatally and postnatally, based on the temporal and regional maturation mediated through a multitude of developmental processes.

Proliferation

Neurogenesis is a highly regulated process that differs depending on the location in the anterior to posterior gradient in the neuraxis. Figure 6 provides a broad overview of the neurogenesis in the major structures of the brain and spinal cord. Bayer et al. (*22*) provide a much more detailed description of the development of specific brain structures. Figure 6 depicts the time during fetal development when neurogenesis occurs in each structure: in other words, when the neurons

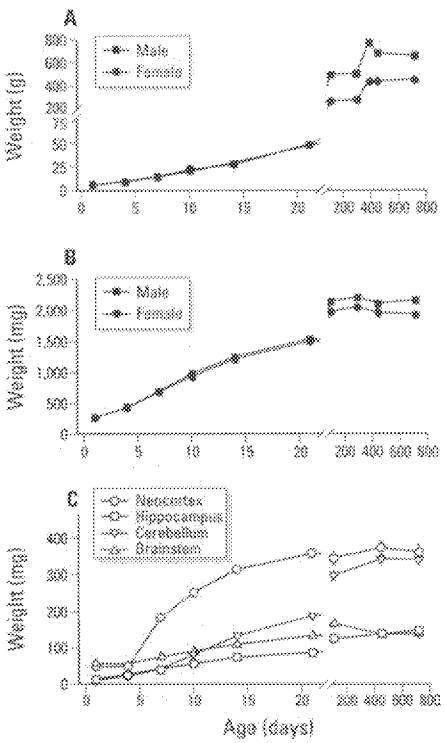


Figure 4. Growth and development can be assessed crudely with measures of (*A*) body, (*B*) brain, and (*C*) regional weights. The data depicted illustrates weights (mass) of female Long-Evans rats during postnatal development. Regional weights are from freehand dissections of each region (brainstem is defined as the pons and medulla). Cerebellum includes both the hemisphere and the flocculonodular lobes. Data are expressed as means ± SE. Adapted from Barone et al. (*20*) and reprinted with permission of Intox Press, Inc.

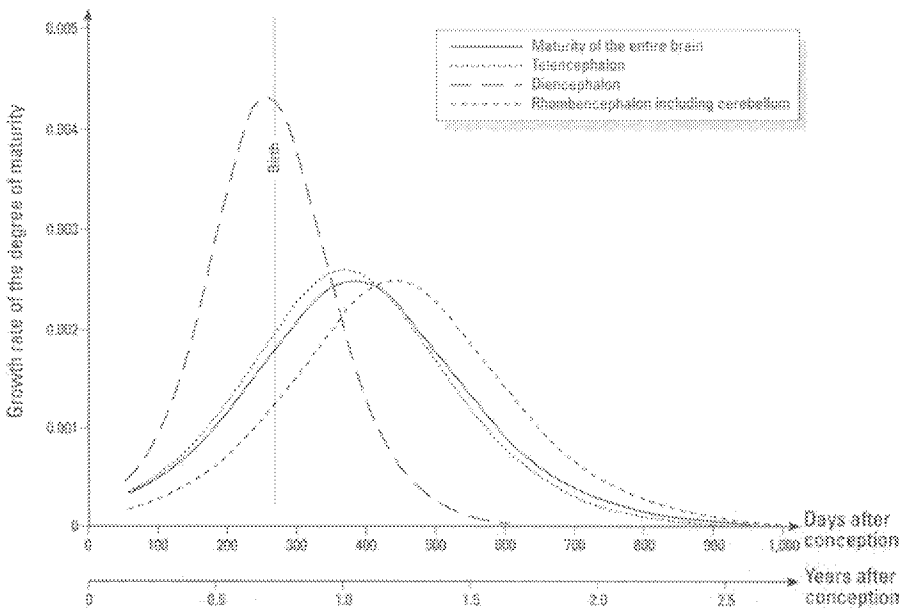


Figure 5. The regional growth rate of the human brain and different regions during prenatal and postnatal development scaled for both days and years after conception. Growth rate of the entire brain, telencephalon, diencephalon, and rhombencephalon including cerebellum during the development of humans. These curves were derived from four-parametric logistic functions. Adapted from Koop et al. (*21*) and reprinted with permission of S. Karger AG.

ED_001854_00010737-00004

which will eventually comprise that structure are born. Within each broad brain region various nuclei and other substructures also develop according to a predictable timetable.

Both the amount and temporal windows of neurogenesis vary within different regions of the brain. These incongruities can be exemplified by comparing the development of three cortical regions: the neocortex, hippocampus, and cerebellum. Cytogenesis in the neocortex is dependent on the exponential proliferation of a multipotent population of pseudostratified cells localized in the ventricular zone, as concluded by the Boulder Committee study of proliferation and neural development (*23*). In the rat, this ventricular zone is histologically distinct beginning around GD 12. Shortly thereafter, the anatomically superficial subventricular zone is distinguishable. This is a secondary proliferative population of cells that also contributes appreciably to the ultimate cell population of the mature neocortex (*24*). The most expansive phase of proliferation in the rat ventricular and subventricular zones occurs roughly between GD 13 and 18, although some neocortical cells may remain mitotic until near parturition in rodents [GD 21/22; reviewed by Bayer and Altman (*25*) and Rakic and Caviness (*26*)]. In addition, interspecies comparisons between rodent and human proliferation and migration demonstrate that the patterns of these processes and the progression of regional development are relatively parallel, although the time scales are substantially different (days for rodents and weeks to months for humans) (*22*).

The hippocampal formation arises from the morphogenetic folding of the medial proliferative zone of the cortical plate to form the subiculum, pyramidal cell fields, and subsequently the dentate gyrus. The dentate gyrus, which forms prenatally, displays continued postnatal proliferation of granule cells in the hippocampal formation of both rodent and humans (*27*). The proliferation of the cerebellum takes place in different phases, with the primary proliferative cells migrating to the rhombic lips of the primordial cerebellum during the fetal period and then migrating to a secondary proliferative zone in the external granule layer of the cerebellum. This secondary wave of proliferation in the cerebellar cortex occurs postnatally in rodents and during the last trimester in humans but also continues postnatally.

Numerous environmental agents can alter neural proliferation. Classic experimental tools for studying the effects of altered developmental proliferation have included administration of antimitotic agents like ionizing radiation [reviewed by Bayer and Altman (*25*)] and methylazoxymethanol (MAM) (*28*) during critical windows of development. Studies with antimitotic agents have clearly demonstrated that when proliferation is actively occurring in a given region of the brain it is vulnerable, but when cell proliferation ceases, the brain is more resilient to these agents. More recently, a number of reports have focused on the effects of ethanol on proliferation in the fetal brain of experimental animals [reviewed by Guerri (*29*)]. The capacity of ethanol to alter proliferation in the ventricular and subventricular zones has been clearly demonstrated in rodents (*30*). The organophosphorus pesticide chlorpyrifos appears to alter proliferation after developmental exposure in rodents (*31–34*). In the case of methyl mercury it appears that proliferation is affected in both experimental animals (*35,36*) and humans (*37*).

Migration

Migration of recently proliferated cells (G_0 cells) from the ventricular zone and other germinal layers occurs radially in the medial/dorsal neocortex and tangentially in other regions of the forebrain such as the olfactory bulb and lateral neocortex (*38*). In the neocortex, for example, the mature cortical plate has histologically distinct laminae, classified as layers I

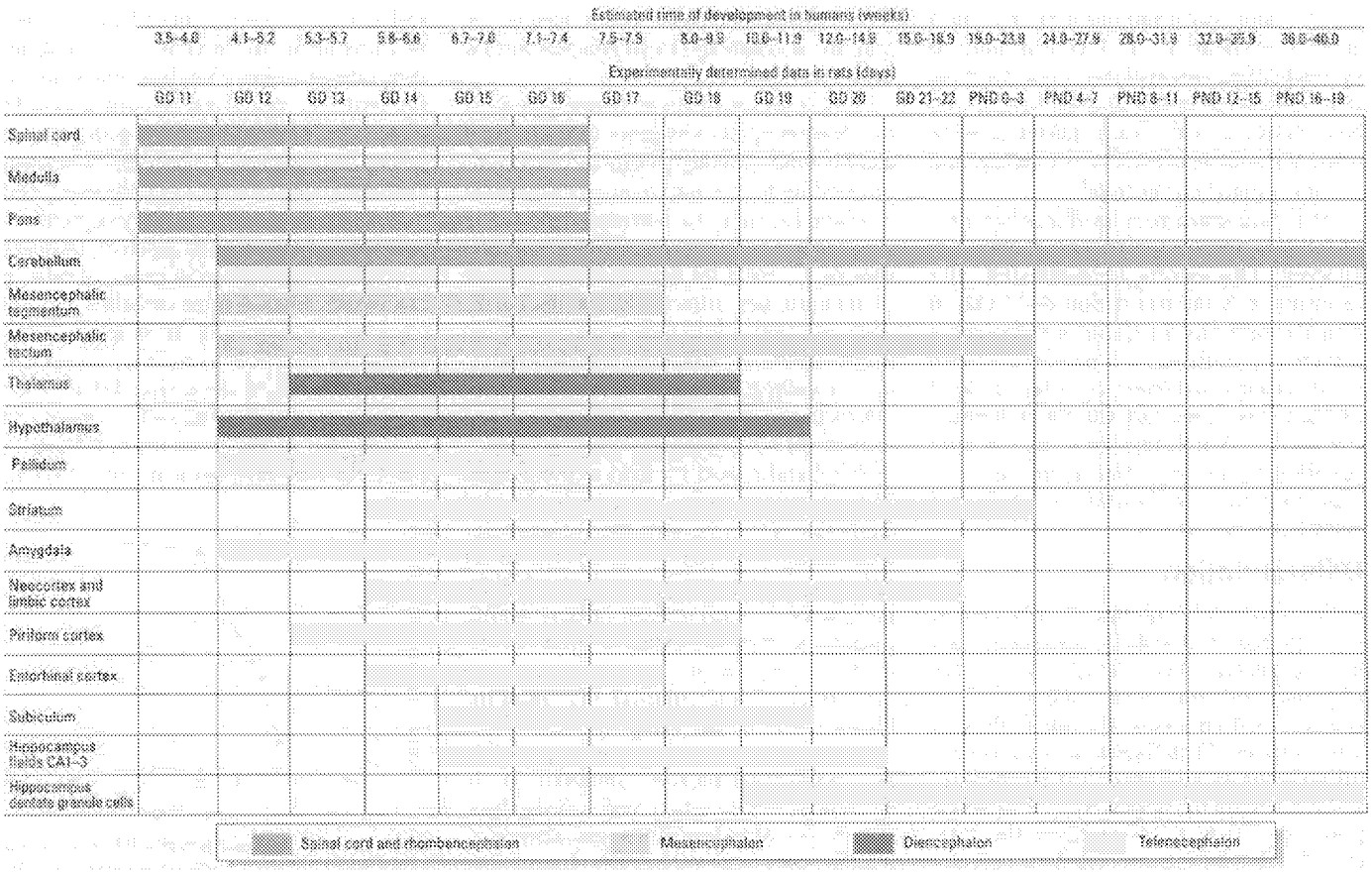


Figure 6. Estimated timelines of regional neurogenesis in rats and humans; shading corresponds to brain vesicle in Figure 3 The scale for rats is in days and the scale for humans is in weeks. Adapted from Bayer et al. (*22*) and reprinted with permission of Intox Press, Inc.

ED_001854_00010737-00005

through VI, and a subplate (layer VII). Layer VI is the deepest layer of the cortical plate; i.e., it is closest to the geometric center of the brain. Layer I is the most superficial layer; it is the outward-most subpial layer. The formation of layers VII and I is distinct from the cell migrations that populate layers VI through II (*39*). Cells from the ventricular zone populate layers VI–II in an inside-out fashion, meaning that the deeper layers form first (*40*). By GD 16 and 17 in the rat, the first cells are arriving in the area that will ultimately form the laminae of the cortical plate. Through the remainder of gestation, the cortical plate gets thicker as more cells migrate from the ventricular zone. In the days before parturition, layer VI is histologically distinct from the remainder of the maturing cortical plate. On postnatal day (PND) 5 of the rat, layers VI and V are readily distinguishable, but layers IV–II are not as clearly defined. These superficial layers (IV–II) are more distinct in adulthood but never constitute more than one-third of the cortical width. The remaining two-thirds of the cortical width is split approximately equally between layers VI and V, depending on the neocortical region of study (*41*). In addition to the migration of neurons to the cortical plate, other factors modify the lamination of the neocortex including cell packing density, cell size, extracellular matrix, gliogenesis, myelination, and synaptogenesis of cortical afferents/efferents, all of which contribute to the final differentiation of this neural structure. In general, these cortical areas are homologous between species, with notable differences in the relative size of structures, cell number, and extent of extracellular neuropil.

It is important to note that when proliferation is disrupted, migration is often also affected. This can be demonstrated after exposure to X-ray irradiation or MAM, in which ectopias are a prominent pathological feature. In addition, a number of known developmental neurotoxicants like ethanol (*42*) and methyl mercury affect both proliferation (*35–37*) and migration (*43,44*) after gestational exposures. Methyl mercury disrupts migration in both humans (*43*) and animal models (*44*).

Differentiation

Differentiation of neuroblasts can be defined as the process of dedicated expression of a terminal phenotype. Even though proliferation, migration, and differentiation are investigated and discussed separately, the initial phase of differentiation likely begins as soon as neuronal precursors complete their last division and are primed for migration to the cortical plate (*45–47*). As neurons migrate, the interplay of extracellular and intracellular cues initiates the expression of particular genes that will influence the neuronal or glial phenotype. Particular phenotypic characteristics such as shape, size, polarity, and expression of neurotransmitters and receptors, among other features, allow distinction among differentiated neurons and glia. Numerous examples appear to support the contention that environmental influences affect this developmental process. Environmental agents that affect differentiation of the nervous system run across a broad gamut of chemical classes including ethanol (*48–51*), nicotine (*52–57*), methyl mercury (*58*), and lead (*59–61*). It is important to note that perturbations that alter neural proliferation and migration often result in altered differentiation. This has been illustrated in studies of punctate exposure to X-ray irradiation in rodent models (*62,63*).

Synaptogenesis

Synapses, the neurobiological substrates of almost all cell-to-cell communication (*64*), mature over the first 3 weeks during the postnatal period in rats (*65*) and through adolescence in monkeys (*66*) and humans (*67*). Synaptogenesis consists of biochemical and morphological changes in both the pre- and postsynaptic elements. Physicochemical compatibility of these elements and correct timing with competitive exclusion of inappropriate connections are essential for the maturation of synaptic connections [reviewed by Jacobson (*65*)]. Within each region of the nervous system, the schedule by which synapses form is rigidly followed.

Direct measurement of synaptogenesis in the developing brain requires ultrastructural analysis which, although highly specific, is only practical under specific conditions where the time and location of a potential alteration of this process is in question. Ultrastructural analysis illustrates the developmental increase in synaptic densities of the rat neocortex [Figure 7 (*68*)]. Other methods of studying synaptogenesis, although less definitive, include indirect approaches such as looking at neurochemical and immunohistochemical markers for synaptic proteins [e.g., synapsin 1 (*69,70*)] and related proteins of presynaptic [e.g., synaptotagmin, synaptophysin, and GAP-43 (*71*)] or postsynaptic origin [e.g., neurogranin and MAP2 (*72*)]. A less direct technique for quantifying synaptogenesis is the morphometric measurement of layer widths. Measurements of the widths of layers that are predominantly synaptic zones (e.g., layer 1 of neocortex, the molecular layers of both the hippocampal dentate gyrus and cerebellum) during early periods postnatally (i.e., PND 10–12) in rats can provide an indirect estimate of alterations in synaptogenesis and dendritic elaboration. Morphometric measurements of synaptic zones in neocortex (*58*), hippocampus (*73*), and cerebellum (*74*) can reveal perturbations of this developmental process.

Exposure during critical periods of development to a number of agents, including MAM (*75*), X-ray irradiation (*76*), ethanol (*77,78*), lead (*79–82*), methyl mercury (*83*), triethyltin (*84*), inhibitors of serotonin synthesis (*85*), parathion (*86*), permethrin, diisopropyl fluorophosphate, and polychlorinated biphenyl (PCB) mixtures (*87*), have all been implicated in altered synaptogenesis. In general, findings from these rodent studies indicate that the effects of these agents are more restricted to synaptogenesis when they are administered postnatally during the first and second week of brain development when this process is occurring rapidly.

Gliogenesis and Myelination

There are numerous supportive cells in the nervous system called glia, including microglia, radial glia, astroglia, oligodendroglia, and Schwann cells, that are integral for the normal development and function of the nervous system (*88,89*). Radial glial and microglial development occurs in parallel with neurogenesis in most structures of the brain, and in the case of microglia may be partially derived from extrabrain sources (*90,91*). Radial glia provide a scaffold for radial migration of neuroblasts (*92,93*). Microglia function as brain macrophages to clean up dead cells and cellular debris after apoptosis (*91*). Oligodendrocytes and astrocytes, on the other hand, develop well after the initial waves of neurogenesis and their differentiation often lags behind that of the neurons in a given structure (*94,95*) (Figure 8). Differentiation of oligodendrocytes follows axogenesis and is believed to be mediated by complex trophic signals between neurons and these glia. Most astrocytes proliferate and differentiate well after much of the migration and differentiation of neuronal cells are completed, although some are believed to arise from the radial glia (*88*). In simplistic terms, astrocytes function to maintain ionic and trophic balance of the extracellular milieu, whereas oligodendrocytes and Schwann cells insulate and myelinate axons of neurons in the CNS and peripheral nervous system,

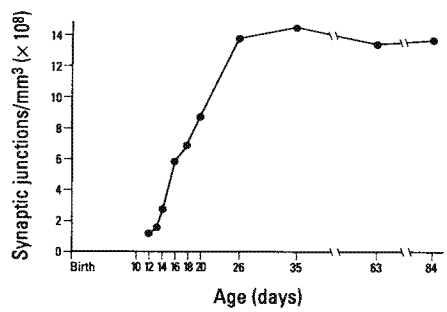


Figure 7. Synaptogenesis determined from ultrastructural analysis of layer 1 of the rat parietal cortex. The *x*-axis scale is in days. Adapted from O'Callaghan (*69*) and reprinted with permission of Raven Press.

ED_001854_00010737-00006

respectively. The functional role of astrocytes and microglia may be transformed after nervous system damage (*96,97*); both cell types become reactive after insults to the nervous system. This reactive gliosis is unquestionably a pathological index when observed in the adult nervous system. In the developing nervous system, neural damage may not initiate the same degree of reactive gliosis depending on the timing of the insult which, in the case of astrocytes, could precede their major phase of proliferation and differentiation. Perturbations of the development of glial proliferation, migration, and differentiation can also result in adverse consequences (*98,99*).

Elaboration of myelin occurs later in development than proliferation and migration of neuronal populations (*100*). Malnutrition can affect myelination, and this process is especially vulnerable during late gestational development in humans and postnatally in rodents. Alterations in myelination can have a persistent adverse outcome resulting from postnatal malnutrition and alterations in thyroid hormone homeostasis even though somatic growth may recover [reviewed by Wiggins (*101*)]. Effects on myelination are readily observed after malnutrition or endocrine disruption during the ontological peak of this process, which occurs in the second week of postnatal development in rats and during the last trimester in humans. However, myelination continues to progress through adolescence in both rodents (*101*) and humans (*102–104*). The protracted time course for this process has also been demonstrated to be vulnerable to perturbation in both rodents and humans. Prenatal and postnatal exposure of rats (*105,106*), and probably late prenatal exposure in humans, to ethanol (*107*) produces significant decreases in myelination and these effects can persist throughout the postnatal period. Similar findings have also been observed after postnatal lead exposure in rats (*108–110*) and developmental exposure in humans (*111*), where delayed myelination was observed during the postnatal period.

Apoptosis

Proper development of the nervous system requires apoptosis, a form of programmed cell death that systematically removes large numbers of neurons in some structures produced during ontogeny. Apoptosis occurs during both pre- and postnatal development of the CNS in two waves. The earlier wave occurs in proliferative zones; the second occurs in postmitotic cells that are both neuronal and glial in phenotype (*112,113*). Apoptosis is distinguished from the other general category of cell death, necrosis, by specific characteristics including maintenance of membrane, chromatin condensation, cell shrinkage, oligonucleosomal fragmentation of DNA, and a general lack of inflammation [reviewed by Bredesen (*114*)]. Cells undergoing apoptosis in the nervous system are targeted asynchronously and removed from the surrounding tissue without stimulation of an inflammatory response. In a region sustaining massive developmental apoptosis, only a small percentage of the cells may be morphologically identifiable as apoptotic at a given time (*115,116*). Thus, characterization of developmental apoptosis may be necessary to understand normal nervous system development and could elucidate how neurotoxic agents perturb this process and result in altered cell number and neural function after exposure (*117,118*). This form of cell death results in less overt pathology than that which would be observed after damage to the adult nervous system but still leads to alterations in cell number and connectivity within the nervous system. Anomalous patterns of this form of cell death may be a consequence of exposure to environmental neurotoxicants. During critical periods, exposure to environmental agents may shift the tightly regulated balance of neurotrophic signals that regulate apoptosis, thereby causing alterations that result in undesirable increases or decreases in cell number in a particular region of the nervous system. Exposure to a number of agents, including ethanol (*119,120*), lead (*121,122*), methyl mercury [reviewed by Nagashima (*123*)], and chlorpyrifos (*33*), promotes this process during development in rodents. Alterations induced by xenobiotics can result in the progressive loss of neurons and may result in compromised neurological function later in life, as is the case in some neurodegenerative diseases (*124–128*). Although apoptosis has been studied in neurodegenerative disease, there has been little work examining the effects of environmental agents on apoptosis in the developing nervous system in humans.

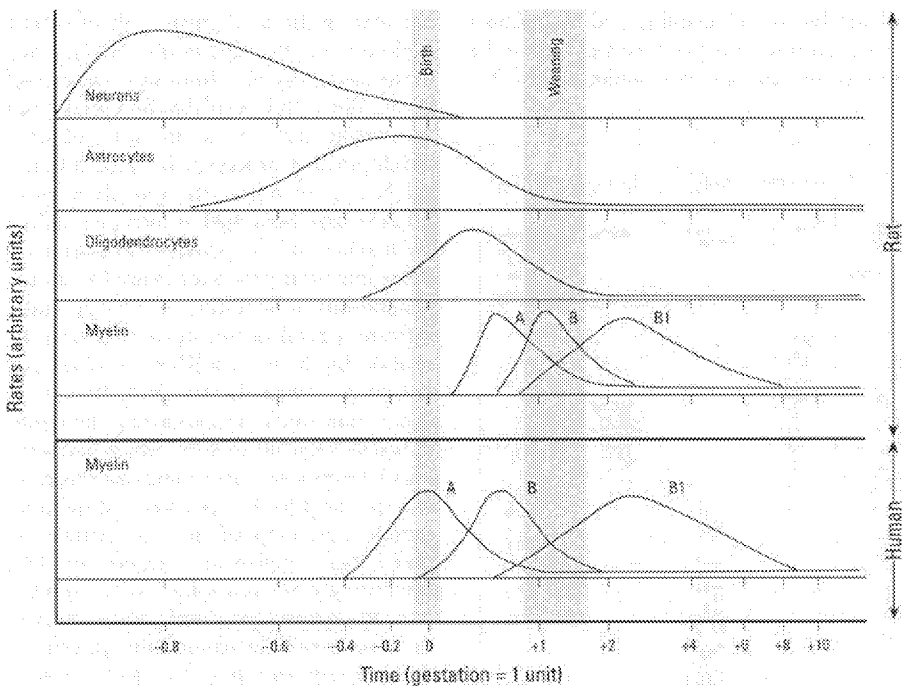


Figure 8. Proliferation of neurons and glia are depicted with the temporal and regional pattern of myelination which occurs later in development. Abbreviations: A, sciatic nerve; B, whole brain; B1, corpus callosum. The schedule of brain development for rats and humans is in arbitrary units (*x*-axis). Adapted from Wiggins (*94*) and reprinted with permission of Intox Press, Inc.

Neurotrophic Signals

Cascading events define the entirety of brain development. The number of molecules involved in modulating neuronogenesis is enormous. The signal transduction of these trophic molecules uses both second and third messengers, which may lead to alterations in gene expression or epigenetic changes via phosphorylation and/or glycosylation of existing signaling and structural proteins. Changes in gene expression and signaling are reflected in cellular processes and events leading to differentiation. The intervening factors that can potentially modulate every step of a signaling cascade further complicate investigation of neuronal differentiation. What follows is a brief discussion of a few individual molecules important in proliferation, differentiation, and apoptosis. Nerve growth factor is the prototypical neurotrophic ligand. This soluble peptide is a ligand for tyrosine kinase receptors and *p75* receptors throughout the developing brain. *In vivo* and *in vitro* investigations have demonstrated that this ligand [reviewed by Klein (*129*) and Zhou and Bradford (*130*)] and other structurally

ED_001854_00010737-00007

homologous neurotrophic factors, including brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4, are important to many processes in neural development [reviewed by Barone (*131*)]. Alterations in the expression or signaling of these trophic molecules result in adverse consequences for both the structure and function of the nervous system (*131*). A number of studies have demonstrated that changes in cell excitability resulting from pharmacological manipulations of many neurotransmitter systems, including glutaminergic (*132–137*), cholinergic (*138–142*), catecholaminergic (*143*), gabaergic (*144*), and peptidergic [opioid agonists and antagonists (*145*)] lead to pronounced changes in neurotrophic factor expression. In addition, a number of environmental chemicals and pharmaceutical agents alter the expression and/or signal transduction of these trophic molecules, including ethanol (*146–152*), methyl mercury (*153,154*), aluminum (*155*), and cholinesterase inhibitors (*138,139,156*). Although neurotrophic factors are perturbed in experimental animals after exposure to environmental agents, the involvement of these factors in developmental disorders has only recently been suggested in humans (*157*).

Neurotransmitters as Morphogenetic Signals

Neurotransmitters and other ligands have qualitatively different functions during development of the nervous system than in the adult organism. In the adult nervous system neurotransmitters are classically thought of as mediating or modulating synaptic transmission across a cleft between two cells. However, during development these same factors may interact with their cognate receptors over a much greater distance and form a morphogenetic gradient that is important in pattern formation of different regions of the nervous system and differentiation of different neurotransmitter systems [reviewed by Buznikov et al. (*158*)]. Developmental ontogeny of the neurotransmitter systems for humans is detailed in Figure 9 (*16*). Some factors that are important for initiating cascades that influence neural development include the neurotransmitters [reviewed by Cameron et al. (*159*) and Chausovsky et al. (*160*)], γ-aminobutyric acid (*161,162*), excitatory amino acids (*163*), opioids (*164–168*), acetylcholine (*169*) and acetylcholinesterase (*170,171*), catecholaminergic agonists and antagonists (*172*), and serotonin (*173*). Because many of these factors are pleiotropic and play fundamentally different roles during development than during adulthood (*174–176*), it would seem prudent to investigate whether pharmaceutics and pesticides (e.g., insecticides, herbicides, and fungicides) that are neuroactive or designed to target specific neurotransmitter systems may have qualitatively different effects than their pharmacological effects observed in adults. For example, effects of the organochlorine pesticide dieldrin on morphogenesis have been observed after exposures in whole embryo culture conditions (*177*).

It is apparent from the summary of these specific developmental processes that ontogeny of different parts of the brain occurs at different times during the prenatal and postnatal period, thus broadening the temporal window of vulnerability and the number of developmental processes that may be affected by exposure to xenobiotics. This has important implications concerning the anatomical, neurochemical, and functional consequences of the timing of exposure to a neurotoxic agent and effects that may be manifested later in life. For example, short-term exposure to a neurotoxicant during week 4 of gestation in humans (or on GD 11 in rats) would be expected to interfere with neurogenesis in the spinal cord and hindbrain structures but not the more anterior structures of the brain. In contrast, toxic insult at the end of gestation in humans or in the first postnatal week in rats might affect neurogenesis in cerebellum and hippocampus, as well as possibly other processes (cell migration, myelination, and synaptogenesis) in areas that have already undergone neurogenesis. Specific effects would depend not only on the timing and duration of the exposure but the processes affected by a specific neurotoxicant. Numerous neurotoxicants can affect the same developmental processes depending on dose and duration. In many cases, these effects on these developmental processes are mediated through very different mechanisms. By inference the effects on the developmental processes reflect downstream convergence on modes of action critical to the normal development and function of the nervous system.

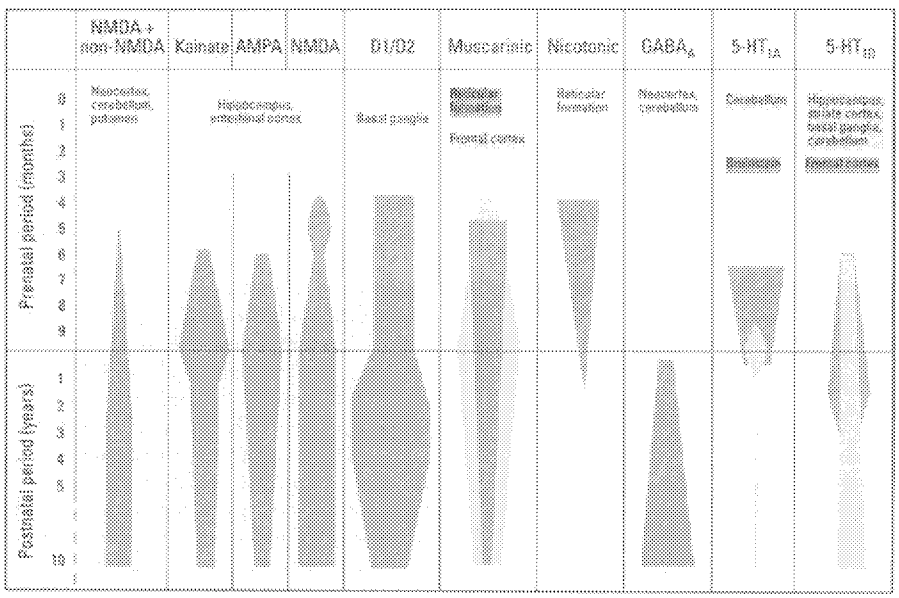


Figure 9. Comparison of regional timelines in the receptors for classical neurotransmitter is depicted for humans. Adapted from Herschkowitz et al. (*16*) and reprinted with permission of Hippokrates Verlag GmbH.

Application of Molecular Biology to Developmental Neurotoxicology

The application of molecular techniques and transgenic technology has many advantages in elucidating the mechanistic role of specific molecules to affect the normal development of the nervous system. In many cases antibodies are not readily available for specific proteins that are used as markers of these developmental processes. In some instances mRNA levels or *in situ* hybridization of mRNAs have been used as surrogate molecular markers of the proteins important to developmental processes. Application and generalization of results of mRNA studies warrant a good degree of caution until the relationship between mRNA levels and protein levels is well characterized. Recent evidence from studies characterizing the normal ontogeny of neurotrophins demonstrates that it may be erroneous to assume that expression of a specific mRNA is predictive of the corresponding protein levels due to posttranscriptional and/or translational regulation (*178*). Interestingly, neurotrophin mRNA levels in one region were not closely correlated with their corresponding neurotrophin protein levels and consequently not predictive of regional neurotrophin protein levels (*178*). In short, molecular approaches may be useful in mechanistic studies and in the context of gene discovery, but unless they are used in

ED_001854_00010737-00008

conjunction with an examination of the protein levels, they may not always prove useful in predicting an adverse effect.

Another approach worthy of attention is the use of knockout and transgenic animal models. These technologies may be useful in demonstrating the effects of regulation of specific molecules during development. Transgenic technologies may also prove useful in understanding the role of genetic polymorphism in response variability when molecular targets are identified. Recent research has identified genetic polymorphisms in a number of enzymes that both metabolize and detoxify xenobiotics, including pesticides (*179*). A particularly salient example is the role of genetic polymorphisms for paraoxonase (*179,180*), an esterase that detoxifies many organophosphorus pesticides. These polymorphisms appear to play a role in response variability in the degree of cholinesterase inhibition. In addition, there appears to be ontogenic development in both rodents and humans that may in part play a role in age-related sensitivity (*2*). However, interpretation of these molecular approaches requires caution when extrapolating the results to developmental toxicology because knockout technology may result in an all-or-none response, which may not be relevant to xenobiotic exposure. Conversely, the toxicological exposure may perturb a molecular mechanism or group of related molecular pathways and thus be more adverse than knocking out or altering one gene product during development.

Neuronal Plasticity

It is important to recognize that the nervous system continues to remodel and change not just early in development but throughout the entire period of development (and even during adulthood) in response to environmental influences as well as genetically programmed events. One mechanism for this remodeling is the normal genetically programmed overproduction and subsequent elimination of neurons and neuronal processes. For example, there has been extensive research on this issue in the rhesus monkey by Pasko Rakic and colleagues (*181*). Synaptic density in primary visual cortex increases until approximately the third postnatal month, then decreases until about 2 years of age, followed by a slower decrease between 2.7 and 5 years of age (puberty) (*181*). The timeframe of synaptic development in monkey cortex is the same for areas including somatosensory, motor, and prefrontal cortex (*182*), suggesting that cell-to-cell communication in the neocortex may be orchestrated by a single genetic or humoral signal. The overproduction and subsequent elimination of neurotransmitter receptors in disparate areas of the monkey neocortex is synchronized with synaptogenesis (*183,184*). In contrast, elimination of neurons in the lateral geniculate nucleus of the thalamus, which is up-system from neocortex, occurs during the middle third of gestation (*185*). These examples demonstrate the elegant and orderly sequence of elimination of neuronal elements during development, which continues at least until puberty. In motor cortex of the monkey, synaptogenesis continues for several months postnatally, and then decreases until approximately 10 years of age (well after puberty) (*186*). Similarly, synaptogenesis in prefrontal (*66*) and somatosensory cortex (*187*) continues into the early postnatal period followed by a slow decline into adulthood. Approximately 70% of the axons in the corpus callosum are eliminated between birth and 4 months of age (*188*).

Environmental input plays a crucial role in the development of the architecture of the brain after birth. The seminal work of David Hubel and Torsten Wiesel, for which they won the Nobel Prize in Physiology and Medicine in 1981, demonstrated significant remodeling of the visual system of kittens in response to deprivation of input to one eye (*189*). The visual cortex was remodeled such that the primary visual cortex consisted of representation from only the unoccluded eye. Further, the kittens appeared essentially blind in the deprived eye when the lid suture was reversed at 3 months of age. Similar results were observed in a series of experiments with monkeys (*190*). Subsequently, numerous studies have documented remodeling of other sensory systems in a number of species in response to experimental manipulation of input into that system (*191–195*). Interestingly, when kittens are deprived of visual input from birth, an area of the parietal cortex normally associated with vision is taken over almost completely by auditory and somatosensory inputs (*196*). Auditory neurons in this area exhibited sharper spatial tuning in visually deprived cats, and these cats could localize sound sources more precisely than nondeprived cats.

Other brain areas also respond to early experience. For example, rearing rodents in enriched environments compared to impoverished or typical laboratory environments resulted in significant increases in cortical thickness, dendritic branching, and synaptic density (*197–200*). Exposure to enriched environments early in development also results in improved performance on learning tasks in rats (*201*). The environment during the first several years of life in humans may also have profound effects on structure and function of the limbic system (*202*), which is critical for social and emotional function.

Neuronal plasticity continues at least throughout childhood and into adolescence. Computational analysis of the brains of children 4–17 years of age revealed an age-related increase in the size of fiber tracts supporting motor and speech functions (*104*) (Figure 10). In an example of remodeling in the somatosensory cortex in response to experience, magnetic resonance imaging (MRI) revealed that the cortical representation of the left but not the right hand of string players was larger than in nonplayers, and that the increase in area was correlated with the age at which individuals began to play (*203*) (Figure 11). Other researchers have also identified continued development of brain structures through late childhood, adolescence, and young adulthood using imaging techniques (*204–206*).

Assessment of Nervous System Function in Animals and Humans

There are a number of standardized clinical tests for assessment of the integrity of nervous system function in the developing human from infancy through the school years. Standardized test batteries such as the Neonatal Behavioral Assessment Scale (NBAS) are available for assessing intactness of the nervous system in young infants, measuring such functions as neuromuscular and motor reflexes, reaction to sensory stimuli, habituation to repeated stimuli, and autonomic function (*207,208*). Assessment of neurological and cognitive development may be performed in children by the use of age-adjusted scales such as the Bayley Scales of Infant Development in very young children, the McCarthy Scales of Children's Ability (MSCA), and the Kaufman Assessment Battery for Children in older children. These instruments include tests for psychomotor, memory, verbal, perceptual, and other components depending on the instrument and age range being assessed. In older children, the Weschler Intelligence Scales for Children - Revised (WISC-R) is typically used to assess cognitive function; this instrument is divided into a number of subscales to partition out various aspects of cognitive performance. Performance on early childhood tests is not predictive of performance on the WISC-R at school age for the general population of children (*209*) but may have better predictive power for low-functioning children (*210*). There has also been some research on the development of play behavior in young children (*211–214*), including the correlation between play and language development (*215*) and coping behavior (*216*). A test that has proved extremely useful in the assessment of the cognitive abilities of infants is the preferential-looking test [Fagan test (*217*)]. This test takes advantage of the fact that an infant looks longer at a novel stimulus (e.g., a picture of a face) than at a familiar one, and so the test can be used to assess short-term memory. If the infant looks longer at the novel

ED_001854_00010737-00009

stimulus than at the one previously presented (preferential looking), it is assumed that the infant remembers the previously presented stimulus. This task is more highly correlated with later performance on intelligence quotient (IQ) tests than sensorimotor tests such as the Bayley Scales (*218*). Preterm infants do less well on tests of preferential looking at 6 and 12 months of age than full-term infants (*219*), a finding that has been replicated in infant monkeys tested at corresponding ages (*220*). Monkeys exposed to methyl mercury *in utero* perform more poorly on this task than do control monkeys (*221*), as do human infants exposed prenatally to PCBs (*222*).

There are other cognitive behaviors that may be tested in very young infants, such as imitation of facial expressions (*223*), a form of cross-modal matching (i.e., visual and sensorimotor). Young infants are capable of cross-modal matching in other modalities as well, such as visual tactile (*224*). Infants also progress through a series of stages of understanding that an object that is no longer in sight still exists (*225*), a cognitive awareness labeled object permanence. A comparison of tests of early cognitive function and later IQ (*224*) revealed a good correlation between preferential looking, cross-modal matching, and object permanence with IQ at 6 years of age. Additionally, results of preferential-looking tests at 7 months of age and cross-modal matching tests at 1 year of age predicted children considered to be at risk for learning disabilities at 6 years of age. Development of object permanence is also retarded in infant monkeys exposed prenatally to methyl mercury (*226*). An assessment of concurrent predictors of IQ in children 6 years of age (*227*) found a high correlation between IQ and tasks that may be performed in animals, including delayed match to sample (DMTS) and conditional discrimination. Another test that is highly correlated with IQ is speed of information processing, including complex reaction time (*228–231*). This test has been used in monkeys to assess cognitive effects of developmental methyl mercury exposure (*232*).

Tests of sensory function, motor function, reflex ontogeny, and learning have been incorporated into a number of behavioral teratology rodent screening batteries like the Cincinnati Psychoteratogenicity Screening Test Battery (*233*), Barlow and Sullivan Screening Battery (*233*), and the U.S. Environmental Protection Agency testing guidelines for developmental neurotoxicity (*234*). These screening batteries were designed with considerable emphasis on apical tests of function during development. Specific tests have been developed to assess the ontogeny of sensorimotor function in the rat, including habituation, reactivity, exploratory behavior, and motor coordination and integrity (*235–238*). Such tests assess many of the same functions as the NBAS and Bayley Scales used with human infants and toddlers. Other early tests of nervous system integrity in rodents may include homing behavior (returning to the nest or siblings), cliff avoidance, placing reaction, passive avoidance, and escape latency on a swimming task. Whereas most of these behaviors show a smooth pattern of development some time during the first 21 days of life (*236*) (e.g., Figure 12), the ontogeny of motor activity and exploration activity displays a more complicated pattern (*235*) (Figure 13). Locomotor activity increases and then decreases during the first 21 days of life, and then increases again after weaning. The decrease in locomotor activity is mirrored by an increase in exploratory behavior during that developmental period. The emergence of locomotor behavior reflects the development of mesencephalic and spinal function, from crawling at PND 10 to an adultlike pattern at PND 15 in rats (*235*). Similarly, the increase and later decrease in exploratory activity is presumed to be reflective of the brain circuits

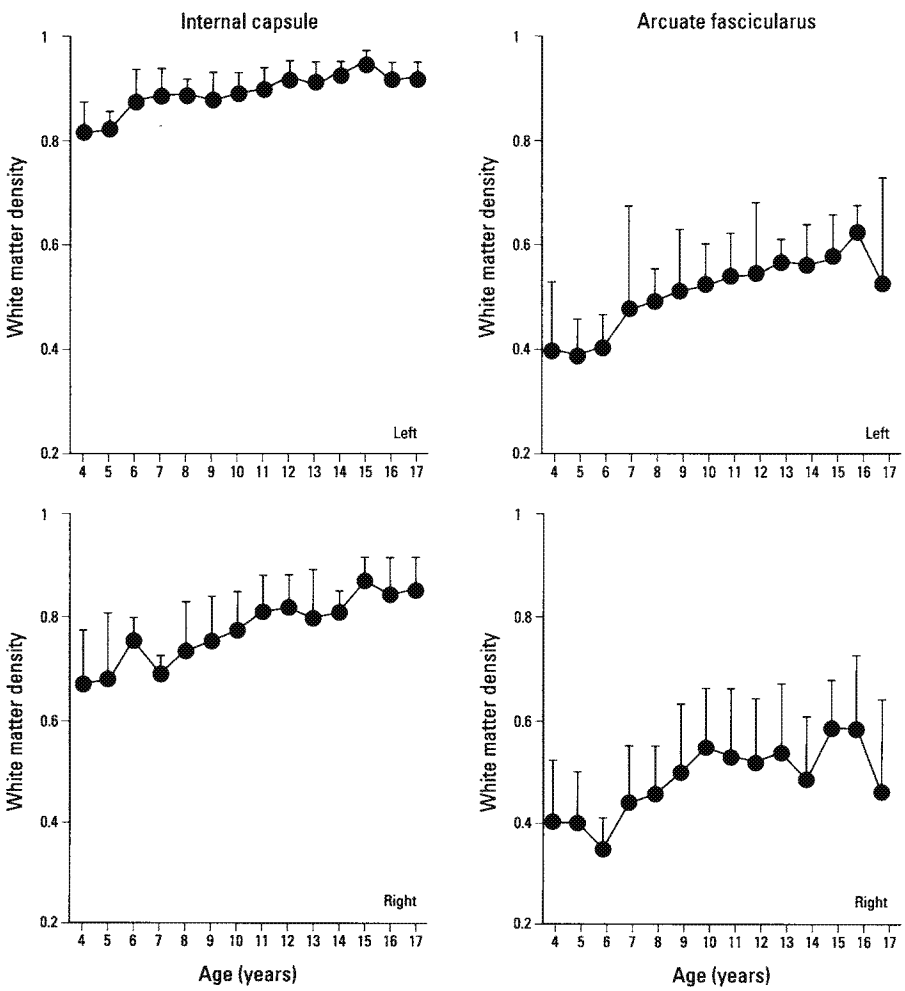


Figure 10. Postnatal myelination in humans, with increasing white matter density for the internal capsule and arcuate fascicularus for 111 children and adolescents ranging in age from 4 to 17 years of age. The internal capsule is a fiber tract involved in motor function; the left arcuate fascicularus subserves speech function. The late maturation of these pathways suggest ongoing increases in diameter and/or myelination of axons at least through adolescence. Adapted from Paus et al. (*104*).

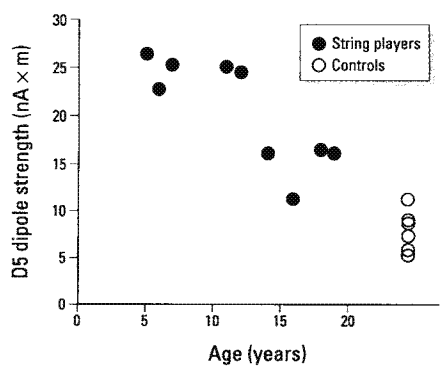


Figure 11. Center of cortical responsivity for tactile stimulation to the fifth (little) finger of the left hand in string players and controls, as measured by MRI. String players had an expansion of the cortical area devoted to the hand area that was correlated with the age at inception of musical practice but not the amount of practice. Adapted from Elbert et al. (*203*).

ED_001854_00010737-00010

"coming online" for attention to and integration of sensory information, followed by the ability to cease to attend to irrelevant stimuli. The ontogeny of specific tasks that rely on hippocampal function and integration with other neural circuits has also been a specific focus for research in the rat (Table 1) (*239*).

A number of tasks may be used in both animals and humans to assess cognitive function. Although some of these are used mostly with monkeys, a number of them can also be used with rodents. Simple visual discrimination tasks, in which the subject must learn which of two stimuli is correct, can be used with many species. An additional requirement that is often imposed is termed discrimination reversal. After the subject learns the task to some predetermined criterion, the positive (correct) stimulus becomes the negative one, and vice versa. This requirement is often more sensitive to disruption by exposure to a toxicant than is the initial acquisition of the discrimination task. Developmental lead exposure produces impaired performance on discrimination reversal tasks in rats (*240*), monkeys (*241*), and children (*242*). Another task that has proved sensitive to developmental neurotoxicant exposure is the delayed alternation task, in which the subject is required to simply alternate responses between two positions on successive trials to be reinforced. Delays between opportunities to respond may be imposed to assess short-term spatial memory. Performance on this task has proved sensitive to developmental lead exposure in rats (*243*) and monkeys (*244,245*). Developmental PCB exposure also produces impaired performance in both species (*246,247*).

The delayed response (DR) task used with monkeys and infant humans is a variant of the delayed alternation task. In this task, the subject watches one of two positions being baited (with food or a preferred toy, for example) and then a delay is interposed during which the subject is prevented from viewing the stimuli. After the delay, a correct response (reach) results in attainment of the reward. As long as the subject's responses are correct, the correct stimulus alternates between two possible positions from trial to trial. In the typical DR task, the correct position continues to alternate irrespective of whether a particular response is correct. Thus, a subject could always respond at one position, left or right, and be correct 50% of the time. In an alternative version of the task, incorrect responses are "corrected"; i.e., the correct position remains on the same side until the subject responds on that side. This task has been much studied in human infants, and is referred to as A not B. Delayed alternation can also be tested as a corrected or noncorrected task.

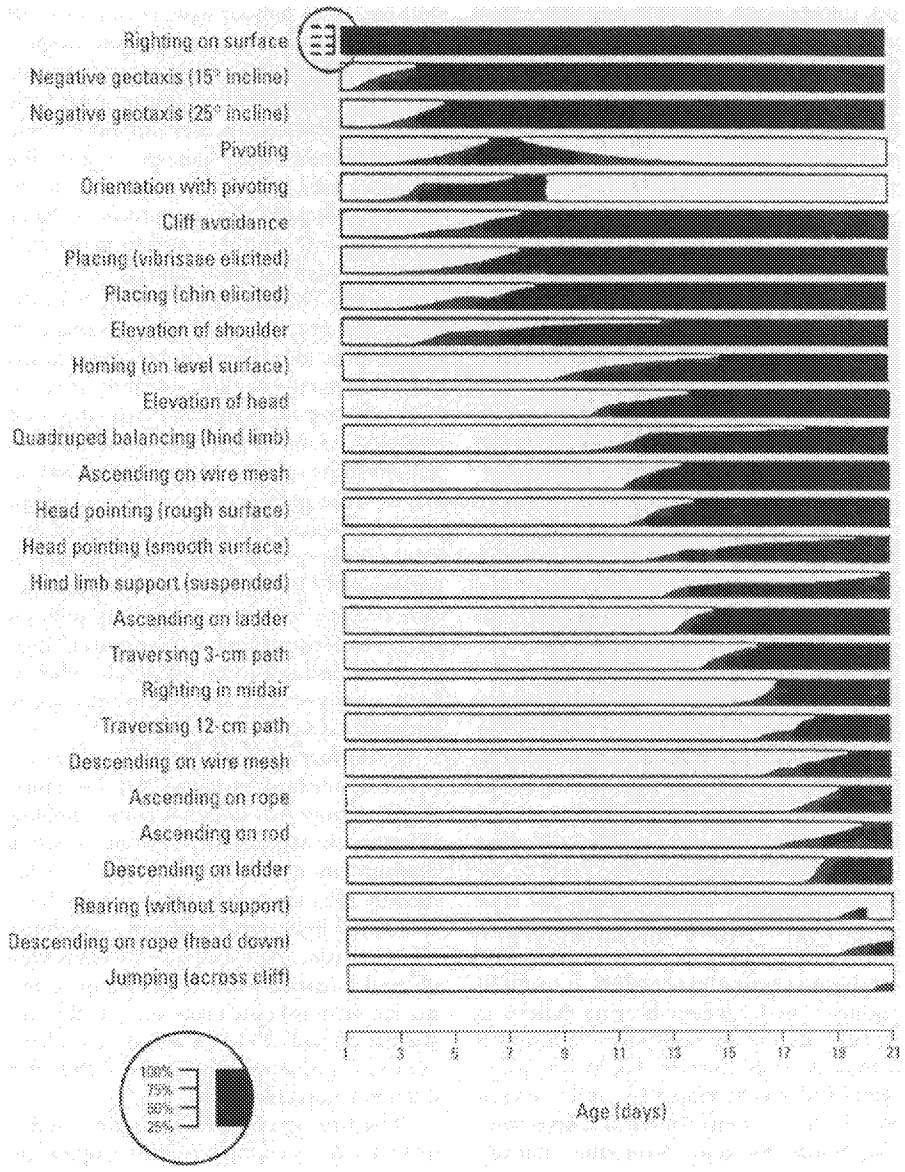


Figure 12. Summary diagram of the emergence of different postural, locomotor, and other related skills in rats. In the majority of instances performances levels (25, 50, 75, and 100 percent) refers to the percentage of rats successful in the display of the response. In a few instances the reference is to a level of performance with respect to asymptotic response frequency. Redrawn from Altman and Sudarshan (*236*) and reprinted with permission of Academic Press, Ltd.

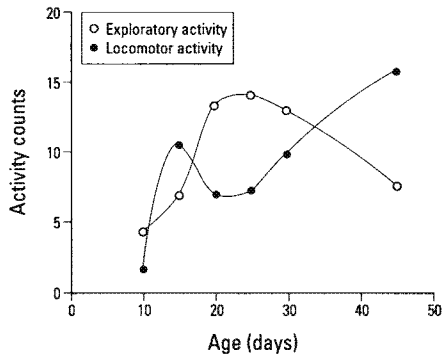


Figure 13. Ontogeny of motor activity and exploratory behavior in rats. Locomotion was measured by crossing of photocell beams in an area 36 × 36 cm. Exploration was measured by number of nose pokes into holes in the floor of the same apparatus. Activity patterns display a complex ontogenetic development, with exploratory and locomotor activity being more or less inversely related. Adapted from Bâ and Seri (*235*) and reprinted with permission of Elsevier Science Ltd.

Table 1. Timetable of hippocampally mediated functions in rats.

Behavioral tasks	Emergence of adult levels of proficiency on PND
Partial reinforcement inhibition	12–14
Olfactory reversal	18
Morris water maze	21–23
Delayed alternation	21–27
Spatial navigation	22–25
Pavlovian trace fear conditioning	25
Habituation to novel stimuli	25–30
Passive avoidance	25–30
Spontaneous alternation	27–30
Latent inhibition	32

Adapted from Bachevalier and Beauregard (*239*).

ED_001854_00010737-00011

Tasks that have been used extensively in monkeys are DMTS and delayed nonmatching to sample (DNMTS). These tasks are also suitable for use with rats and have been used to study the ontogeny of specific brain regions in human infants. In the DMTS, the subject is presented with a stimulus, which is then withdrawn. After a delay, which may vary from trial to trial, the subject is presented with the previous stimulus plus one or more additional stimuli and must choose (match) the previously presented stimulus. In the DNMTS, the subject must choose the novel (nonmatch) stimulus from a pair of stimuli. The DNMTS is typically easier to learn because test subjects prefer a novel to a familiar stimulus. This task has been used in both children (*227*) and monkeys [reviewed by Webster et al. (*248*) and Murray and Mishkin (*249*)]. The DMTS task has proved sensitive to disruption by developmental lead exposure in monkeys (*250*).

Intermittent schedules of reinforcement have been used extensively in behavioral pharmacology and toxicology to assess the effects of environmental agents on behavioral function (*251*). On an intermittent schedule of reinforcement, the subject is reinforced according to a set of rules: for example, after emitting a certain number of responses (fixed ratio), or for the first response after a specified period of time that remains constant from one reinforcement opportunity to the next [fixed interval (FI)]. Although only one response at the end of the interval is required for reinforcement, FI performance is typically characterized by a gradually accelerating rate of response terminating in reinforcement; both the temporal pattern of responding and the rate of response may be modified by exposure to a toxicant. The FI schedule has proved particularly sensitive to developmental exposure to such agents as lead, PCBs, methyl mercury, and pesticides in both rats and monkeys (*252–260*). Performance on other intermittent schedules has also proved sensitive to disruption by developmental toxicant exposure (*261*).

An issue that is of particular importance in the design of animal behavioral studies is whether each task is assessed independently in experimentally naive animals or whether a series of tasks is presented sequentially to the same subjects. Children are of course required to build knowledge and skills sequentially, necessitating transfer of learning in virtually all aspects of life. In contrast, many developmental toxicology studies of learned behavior in rodents use a separate set of subjects for each task or the same set of animals for at most a couple of tasks. Primate research, in contrast, necessitates testing the same cohort of subjects on many tasks to maximally utilize an expensive and valuable resource. Whether failure to assess cumulative learning misses an important aspect of childhood experience is an important question. In a direct comparison using a rat model of maternal phenylketonuria, it was determined that the requirement for cumulative learning on a series of related tasks revealed treatment-related deficits that were absent when each task was assessed in a naive group of animals (*262*). This is consistent with the finding that one of the characteristics of humans with low IQs is an impairment in the ability to transfer learning from one situation to another (*263*). Therefore, low performance on an IQ test may be viewed as reflecting an accumulated deficit as a result of years of failure to transfer and integrate previous experiences. This issue is also relevant to the findings from longitudinal prospective studies assessing the behavioral consequences of developmental exposure to toxicants. For example, the apparent cognitive decrement produced by lead may become more apparent as the child gets older [reviewed by Rice (*264*)]. Similarly, cognitive impairment was not identified at 18 months of age in a cohort of children exposed *in utero* to PCBs (*265*) but was manifest at 42 months in the same cohort (*266*). Some of the apparent increased sensitivity undoubtedly results from the more informative assessments possible as the child develops; however, an inability to build on previous learning may also play a part.

Assessment of sensory system function may be performed in much the same manner in humans and experimental animals. Sensory-evoked potentials can be measured easily in both rats and humans, as well as other species. Exposure to environmental agents may produce similar effects on visual-evoked potentials in pigmented rats and humans (*267*). Changes in auditory-evoked potentials have been demonstrated in different populations of children as a result of developmental exposure to methyl mercury (*268,269*) or lead (*270*). The reflex modification auditory procedure relies on the fact that an animal will startle (jump or flinch) when presented with an intense stimulus, and that this effect is attenuated if a stimulus detectable to the animal is presented approximately 100 msec beforehand. This procedure can therefore be used to determine sensory thresholds. This paradigm revealed that exposure to PCBs produces low-frequency hearing deficits in rats (*271*) during the early postnatal period of cochlear development. Psychophysical assessment, in which the subject is "asked" to indicate whether or which stimulus is detectable, is appropriate for humans and other animals. Such procedures have been used to assess function in visual, auditory, or somatosensory systems in rats, monkeys, and humans after toxicant exposure (*244,272–275*).

Neurobiological Substrates of Function

All of the major brain structures in humans are also present in rodents and subserve roughly the same functions. The brain stem is mostly responsible for autonomic functions, arousal, and sleep–wake cycles. Some mesencephalic structures may also be involved in cognitive processes in addition to attentional ones (*276,277*). The cerebellum subserves motor function and motor learning (*278*); its role in cognitive processes has only recently been characterized (*279,280*). Specific areas of the basal forebrain are involved in motor function as well as some types of learning.

It must be borne in mind that all brain areas have multiple reciprocal connections, forming circuits subserving various functions. For example, sensory association areas are connected to other areas of neocortex responsible for higher order cognitive function. Cortical and subcortical motor areas form numerous connections, and also form circuits with prefrontal cortical and sensory areas. It is generally believed that there are at least two different forms of memory processes, based on studies in monkeys and humans with amnesia resulting from damage to specific brain areas. These are labeled variously by different authors and include habit versus nonhabit, procedural versus declarative, and reference versus working memory (the last typically by investigators working with rodents). Habit is generally believed to be subserved by a corticostriatal circuit (which seems to be present very early in infancy), whereas nonhabit memory is subserved by a corticolimbic circuit [which develops later in infancy (*239*)]. Damage to a particular structure in the circuit or a connecting pathway may produce structural or functional changes upstream or downstream and result in behavioral changes that are a consequence of damage to the circuit as a whole.

It is clear that the basal forebrain is involved in habit formation (*281*): i.e., procedural memory that does not require holding information temporarily "online," such as discrimination tasks or motor skills. It has recently been argued that the basal forebrain is involved in both habitual and nonhabitual responses (*282,283*). Lesions of various areas of basal forebrain produce deficits in performance on nonhabit tasks such as delayed alternation and DNMTS as well as on habit tasks such as discrimination reversal and other discrimination tasks.

The limbic system consists of medial temporal lobe structures including hippocampus, amygdala, and surrounding cortical structures. Researchers using the rodent as the experimental subject have probably studied the function of the hippocampus more than

ED_001854_00010737-00012

any other brain structure involved in learning and memory, perhaps because the hippocampus in the rodent is relatively large and easy to identify cytoarchitectonically. The hippocampus is involved in spatial memory in both rodents and primates and is also critical for very short-term memory storage, at least in monkeys (*284*). It is unclear whether the deficits observed on such nonhabit tasks as delayed alternation (DA), DR, and DNMTS are the result of lesions of only the hippocampus, the hippocampus plus amygdala, and/or the surrounding entorhinal and perirhinal cortex (*281,285–288*).

The neocortex is divided into areas subserving a number of functions in both rats and primates, including humans [Figure 14, (*289,290*)]. Specific areas are devoted to motor function and the various sensory systems, including visual, auditory, and various somatosensory modalities. These functional areas are further subdivided into primary cortex, which receives input directly from the corresponding thalamic nucleus, and various areas upstream that are responsible for integration and higher order processing. This explanation is a simplification: there is some thalamic input to nonprimary sensory cortex as well, but the bulk of thalamic input is to primary cortical areas. Perhaps the biggest difference between rodents and primates (including humans) in terms of sensory system structure and function is the fact that primates are highly visual animals, whereas the rodent relies heavily on auditory and olfactory cues (as well as tactile cues from the vibrissae) for information about the world. Consequently, approximately half of the primate brain is devoted to visual areas, including higher order processing and integration areas. In contrast, only a small part of rodent cortex is devoted to vision. The visual function of primates is also more highly developed than that of the rodent, with excellent color discrimination and spatial resolution, of which the rodent has neither [Figure 15 (*291*)]. The rodent therefore has considerable limitations with respect to utility for the assessment of visual function, although there are certain aspects of visual structure and function shared between the species (e.g., low-light-sensitive rod-mediated visual pathways). The presumed relative unimportance of visual information compared to information from other sensory modalities in rodents also has implications for testing paradigms: the stimuli used for assessing cognitive function in rodents are typically visual stimuli, probably in part because they are easy to control and in part because we are visual animals. It would seem preferable to use olfactory cues when assessing cognitive abilities in rodents (*262*). It should also be emphasized that both the visual and auditory systems of albino animals of all species are abnormal (e.g., Figure 15); therefore, albino rats or mice are a poor choice for assessment when the nervous system is of interest.

Undoubtedly, the most obvious and important difference between the rodent and human brain, structurally and functionally, is the tremendous relative size and functional importance of the prefrontal cortex (PFC) in humans. Homologous areas of PFC between species are typically defined by projections from specific thalamic nuclei. By that criterion, the rat has a defined PFC that may be subdivided into a number of areas (*292*). The primate cortex, including that of the human, is also divided structurally and functionally into a number of specific areas (*293,294*). The PFC in primates is considered necessary for so-called executive functions (*283,295,296*), including organization of behavior in time and space, planning, inhibition of inappropriate actions (impulse control), ability to change strategy (set-shift), and emotional control. It has been suggested that attention deficit hyperactivity disorder is largely a dysfunction of prefrontal cortical function (*297*). It has also been postulated that damage to prefrontal cortical areas underlies the behavioral impairment produced by developmental lead exposure (*298*). Lesions of various specific areas of PFC in monkeys produce deficits in DA and DR, DMTS and DNMTS, and discrimination tasks. Such lesions also result in impairment in the ability to inhibit inappropriate responding, perseveration, and distractibility. At least some of these same functions (e.g., inappropriate responding and perseveration) are impaired after PFC lesions in rats (*299*). However, behavioral toxicologists using rats as the experimental model have generally not focused on PFC as a possible site of toxicant-induced damage.

An approach that has proved extremely fruitful in the study of the development of cognitive processes and the brain structures subserving these processes in human infants is the assessment of infants on tests used in adult and infant monkeys, and for which the brain structures and circuits necessary for performance of the specific tasks have been delineated. One brain area that has received a considerable amount of attention with respect to ontogenetic development is the PFC. Lesion studies in monkeys have identified a number of tasks that are heavily dependent on various areas of prefrontal cortex, including DR, A not B, DA, and DMTS and DNMTS (*300–302*). Both infant humans and infant monkeys develop the ability to perform these tasks relatively late: over the course of the first year of life in monkeys (*303,304*) and over the first 3 years or so in humans (*305,306*), thereby suggesting a relatively long maturation time for prefrontal cortex. In fact, development of PFC may

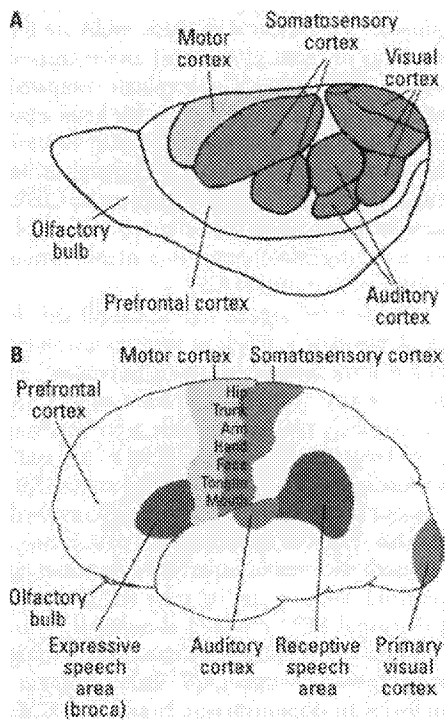


Figure 14. Lateral view of functional areas of the (*A*) rodent and (*B*) human cerebral cortex. The lateral view of the rodent neocortex is redrawn from Kolb and Tees (*289*) and the lateral view of the human neocortex is redrawn from Heimer (*290*). Reprinted with permission of Springer-Verlag.

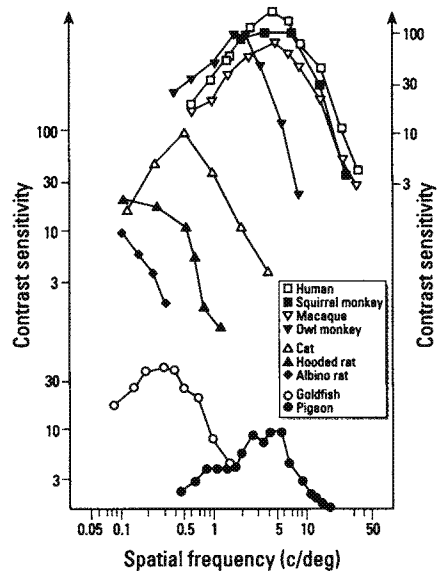


Figure 15. Comparison of spatial visual function in various species. Abscissa: spatial frequency. Ordinate: contrast sensitivity = reciprocal of contrast, which is a function of the difference between the light and dark bars of a series of parallel bars. The visual function of the albino rat is least like that of humans (note three scales of the ordinate), whereas the contrast sensitivity of many nonhuman primates are virtually identical to humans. Adapted from Uhlrich et al. (*291*) and reprinted with permission of The MIT Press and Elsevier Science B.V.

ED_001854_00010737-00013

continue beyond puberty in both species. In contrast to performance on tasks dependent on PFC, habit formation tasks such as discrimination tasks, which are dependent on corticostriatal circuits, are performed at adult levels of competence in both monkeys and humans during early infancy (*304,307,308*).

Another brain circuit for which ontogeny has been studied is the limbic system, including hippocampus, amygdala, and surrounding entorhinal and perirhinal cortex. The hippocampus develops perinatally in the rat but prenatally in humans or monkeys during the last trimester. For example, 15% of cells in the dentate gyrus of a rat are present by birth, compared to 80% of the cells present in the monkey at birth (*308*). In humans, the volume of the hippocampus is fully mature at 15 months, whereas the PFC does not reach adult volume until 10 years of age. Preferential-looking performance is developed at 4 months of age in humans and 2 weeks of age in monkeys (*307,308*). Lesions of the hippocampus result in impaired performance on this task, evidence that this structure matures early in primates (*309*). Lesions of hippocampus in young monkeys also result in deficient social interactions early in life, which become more severe during adulthood (*310*). There is evidence of differences between the sexes in the development of different brain areas as revealed by differential performance on specific behavior tasks in young monkeys (*311–313*) and humans (*312*) that are not present later.

Clinical Consequences of Errors in Developmental Processes

It is well established that being small for gestational age (SGA) is a risk factor for behavioral and other health problems. For example, in a prospective cohort study of 1,037 children, SGA children scored lower on tests of intelligence when tested repeatedly between 3 and 13 years of age (*314,315*). Parents reported more behavioral problems at 15 years of age in the SGA group (*315*). Being SGA presumably results from a suboptimum prenatal environment, and may be an indication of poor overall nutrition, specific nutritional deficiencies, or other factors including exposure to a toxicant. Neurotoxic agents including alcohol, maternal cigarette smoking, PCBs, and perhaps lead all may produce intrauterine growth retardation. It has been argued, at least with respect to lead, that controlling this factor in the statistical analysis represents over-controlling. Prematurity may also produce retarded development. In a study following a group of children from birth to 5 years of age (*316*), premature infants initially lagged behind full-term infants on age-appropriate measures including the Bayley Scales, Stanford-Binet, and MSCA, even when results were age-corrected. By 5 years of age, the premature infants had caught up on most, but not all, measures.

Functional abnormalities of the nervous system and their underlying structural and neurochemical abnormalities may provide important information relevant to normal development, as well as perturbations that may be produced by neurotoxic agents. Schizophrenia is a devastating mental illness that probably has both genetic and environmental causes. Although the identical twin of a person with schizophrenia has a greatly increased risk of developing the disease, the risk has an odds ratio < 1.0, indicating that environmental influences also play a part in the etiology. For example, obstetric complications or maternal influenza during pregnancy are associated with an increased risk of schizophrenia (*317–319*).

There is compelling evidence that schizophrenia is a consequence of errors in developmental processes (*320*) based on the types of abnormalities observed. Many major psychoses, including schizophrenia, become manifest at the end of adolescence and in early adulthood. The period of adolescence is a time of high synaptic density in all higher primates, including humans (*321*) (Figure 16). Thereafter synaptic density decreases in all areas of cortex. Recent studies using MRI (*322*) suggest excessive elimination of dendrites and axons of prefrontal cortex of schizophrenics. Consistent with these results are the findings of reduced neuropil and increased density of neurons per unit volume compared to controls in PFC (*323*) and other brain areas of schizophrenics (*324*). Significant volume loss has also been reported in temporal cortex (*325*) and frontal lobe of schizophrenics (*326*), as well as a greater increase in ventricular volume during adolescence in schizophrenics compared to controls (*327*).

It has been argued that schizophrenia is fundamentally a deficit in working memory, and that the disorganized thought processes in schizophrenia patients result from an inability to accurately retrieve symbolic representation from long-term memory and hold it "in mind" for use in the absence of external cues (*328*). Various areas of PFC are intimately involved in this type of information processing. Research with noninvasive methods including positron emission tomography scanning and functional MRI revealed abnormalities in function in PFC of schizophrenics performing working memory tasks (*320*), including abnormalities in dopaminergic function (*329*). Alternatively, it has been argued that abnormalities of medial temporal lobe, particularly hippocampus, are intimately involved in the pathogenesis of schizophrenia (*330*).

Dyslexia is another mental disability in which specific abnormalities of development are observed. Dyslexia is associated with neuronal ectopias and architectonic dysplasias in various areas of the cerebral cortex (*331,332*) as well as other structural abnormalities. In addition, people with dyslexia have a lack of asymmetry in the planum temporale, a language region on the superior surface of the temporal lobe that is asymmetrical in nondyslexic individuals (*331*). Dyslexics are also more likely to have autoimmune disorders and an increased incidence of left-handedness (*333*). Autoimmune strains of mice have been developed that also have cerebral ectopias and aberrant cortical lateralization (*334,335*), which are of genetic origin. These mice also show differences in various tests of spatial learning, which may be modified by environmental enrichment (*336*).

Epilepsy is a nervous system abnormality that in some cases has a developmental etiology. A large program studying the causes of epilepsy has been ongoing in Rochester, Minnesota, since 1975 (*337*). From that large database it is estimated that approximately 5% of epilepsies have a developmental origin. One-third of children with severe mental retardation or cerebral palsy (CP) also have epilepsy. Perinatal events such as repeated or prolonged febrile seizures may result in epilepsy, and there is evidence for genetic causes for epilepsy in some families. CP is associated with abnormalities of pregnancy and birth, particularly birth asphyxia and low birth weight (prematurity) (*338*). Cranial ultrasound

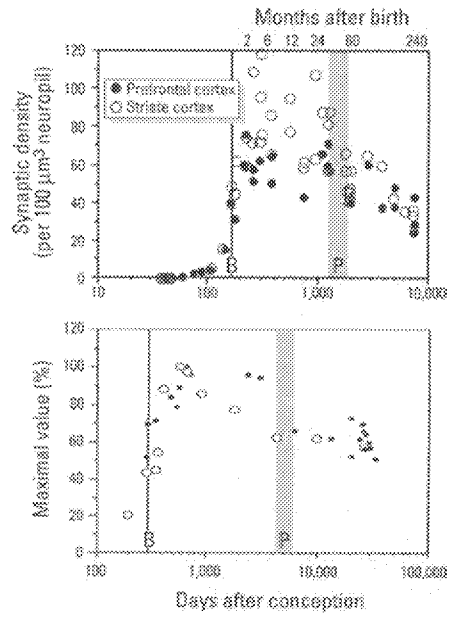


Figure 16. Developmental ontogeny of synaptic density for monkey (top) and human primary visual cortex (area 17 or striate cortex) or prefrontal cortex (area 46 in monkeys). Abbreviations: B, birth; P, puberty. Data in the bottom panel are normalized as a percentage of the maximal value of the curve. Adapted from Rakic et al. (*321*) and reprinted with permission of Elsevier Science B.V.

ED_001854_00010737-00014

imaging in preterm infants may reveal patterns of neonatal brain damage that are highly predictive of later CP: specifically, echodense regions that presumably reflect ischemic or infarctive lesions of the white matter. CP may in some instances result from disorders of neuronal migration (*339,340*) or periventricular white matter damage that may arise during weeks 28–35 of gestation (*339,340*).

Autism is a developmental abnormality that is characterized by impairment of social interaction, limited activities or interests, and deficiency or abnormality of speech development. Autism occurs with a prevalence of 1.3 per 1,000 births (*341*). Although there is a strong genetic factor in autism, it is not heritable in a simple fashion, and environmental factors also play a role. In an insightful piece of detective work, Strömland et al. (*342*) observed that in the Swedish thalidomide registry, there were several patients with autism who had all been exposed to thalidomide between GD 20 and 24. This time period corresponds with closure of the neural tube and production of the first neurons that form the motor nuclei of the cranial nerves. Moreover, these individuals also had ear malformations and hearing deficits, providing further evidence for damage in this short window during gestation. Rodier et al. (*343*) reproduced the major features of the neuropathological syndrome of autism using valproic acid in mice because mice are not sensitive to thalidomide-induced teratogenicity. These abnormalities are also observed in mice in which the *hox-A1* gene is lacking (*344–346*). The *hox-A1* gene is present in humans (*347*), although the consequences of alterations in expression and/or signaling through either genetic mutations or exposure to environmental agents is an area in need of further research.

Long-Latency Delayed Neurotoxicity

An issue that is of considerable concern to neurotoxicologists, and which has great relevance to risk assessment, is the potential for agents to induce delayed neurotoxicity years after cessation of exposure, including exposure during development. The possibility of delayed neurotoxicity stems from at least two scenarios. In one scenario, the ontogeny of a particular function occurs late in development and the manifestation of pathological changes is not revealed until the function in normal animals is apparent. A second scenario involves a developmental insult in which both anatomical and/or functional effects may be masked or attenuated due to neuronal compensation or plasticity, resulting in apparently transient effects that may nonetheless have later sequelae. The possibility of an interaction between aging and exposure to neurotoxic agents is also of critical concern: this possibility was postulated 2 decades ago (*348*) and has been raised repeatedly since (*349,350*). As the normal brain ages, there is a decrease in the number of cells in certain regions, as well as a decline in neurotransmitter levels and repair mechanisms. If this process were accelerated by chronic or historic exposure to a neurotoxicant, the effect as the individual aged would be a further decrease in functional capacity from that typically observed during aging. Alternatively, damage that decreased the reserve capacity of the brain at any point in life might also hasten the appearance of functional deficits.

This phenomenon has been demonstrated in both animal models and in humans. In rodents, latent neurotoxicity has been demonstrated after developmental exposure to X-ray irradiation (*351*), methyl mercury (*352*), and triethyltin (*73*). Developmental exposure to triethyltin produced damage to cortical structures of the nervous system and transient deficits in spatial learning. Apparent compensation at the anatomical level was evident, with some reactive synaptogenesis from surviving cells in the entorhinal cortex and a recovery from spatial learning deficits during adulthood. However, when littermates were examined morphologically and functionally during aging, decreases in synaptic densities and deficits in spatial learning became apparent, providing empirical evidence for accelerated aging as a result of developmental exposure (*73*).

There is both epidemiological and experimental evidence that exposure to the environmental contaminant methyl mercury can produce delayed neurotoxicity (*353*). Methyl mercury toxicity is largely characterized by abnormalities in motor function and impairment in the visual, auditory, and somatosensory systems. As early as 1975 it was recognized that manifestations of Minamata disease (MD) could worsen over time even after cessation of exposure to methyl mercury (*354,355*). A study in Japan including > 90% of persons diagnosed with MD and age-matched controls identified deficits in the ability of persons with MD to independently eat, bathe, use the toilet, dress, and wash their faces (*356*). The relative deficit between controls and people with MD increased with age in a statistically significant manner even though exposure to methyl mercury had ceased in all individuals 20–30 years before assessment.

Delayed neurotoxicity has also been observed in monkeys exposed developmentally to methyl mercury. Monkeys exposed to methyl mercury from birth to early adulthood developed clumsiness beginning in middle age (*357*), which was probably a consequence of somatosensory dysfunction (*358*). This cohort of monkeys, as well as a cohort exposed to methyl mercury *in utero* through puberty, developed deficits in fine motor control during middle age (*353*). The group of monkeys exposed *in utero* through puberty displayed exacerbation of auditory impairment as they aged (*359*). Individuals in both cohorts developed constriction of visual fields during old age that had not been present when they were younger (*360*).

An interaction between aging and neurological disease during childhood has also been observed. It has become apparent over the last decade that up to 25% of people who had contracted polio as children had apparently recovered and were functioning normally, then suffered a recurrence of clinical symptoms as they moved into middle age. Evidence of degeneration in peripheral nerves of these individuals was detected; this may reflect premature senescence of nerves compromised during the acute phase of the disease, or accelerated aging produced by increased metabolic demands on spared normal nerves. Exposure to the polio virus during childhood may also result in the development of motor neuron disease decades later (*361*).

The potential consequences of an interaction of developmental exposure to a neurotoxic agent and acceleration of the aging process are profound. As the large cohort of baby boomers ages, the costs of neurological or psychological dysfunction will be significant, and any added increase in dysfunction as a consequence of exposure to neurotoxic agents may be expected to place additional burdens on the cost and infrastructure of the health care system.

Antisocial Behavior Associated with Early Neurotoxic Exposure

Another form of latent consequences after developmental exposure to neurotoxic agents is exemplified by magnification of early deficits with maturation to adulthood. There is increasing evidence linking aggressive and criminal behavior with decreased IQ (*362,363*) as well as with other deficits typical of exposure to neurotoxicants, such as impulsivity and poor executive control. In a study of aggressive and nonaggressive adolescent boys, the best predictor of aggressive behavior was deficits in executive function (*364*). Children diagnosed with hyperactivity disorders have increased incidence of depression and aggression at 17–18 years of age (*365*), whereas individuals with various psychiatric disorders are at increased risk for criminal behavior (*366*). There is also increasingly compelling evidence for an association between aggressive behavior during childhood and later increased criminality in males, but not females, as a result of developmental exposure to neurotoxicants. Determination of such long-term effects requires long-term follow-up of cohorts in which exposure during development was

ED_001854_00010737-00015

determined. Three toxicants have been studied long enough to perform such assessments: lead, alcohol, and cigarettes. Exposure resulting in an increased body burden of lead was largely postnatal, whereas maternal alcohol consumption or cigarette smoking resulted in prenatal exposure to the fetus. All three agents produce deficits in IQ, attention problems, increased impulsivity, and deficits of executive function. All three are also associated with increased criminality during adulthood as a result of developmental exposure.

Consequences of Developmental Lead Exposure

An association between lead exposure and antisocial and other problem behaviors has been identified in children as young as 2–5 years of age (*367,368*). In a study in children 8 years of age, tooth dentine lead levels were associated with total scores of problem behavior on the Teachers Report Form of the Child Behavior Profile (*369*). Tooth lead levels were also associated with internalizing (consisting of scores for anxiety or withdrawal) and externalizing (consisting of inattentive, nervous-overactive, and aggressive scores). There was also a weak association between tooth lead levels and prevalence of extreme problem behavior scores.

The consequences in older children of this poor social adjustment were explored in a retrospective cohort study of the association between bone lead levels and measures of social adjustment in boys at 7 and again at 11 years of age (*370*). At 7 years of age, borderline associations after adjusting for covariates were observed between teachers' ratings and lead levels for aggression, delinquency, social problems, and externalizing behaviors on the Child Behavior Checklist (CBCL). When these children were 11 years of age, parents of subjects with higher lead levels reported significantly more somatic complaints, more delinquent and aggressive behavior, and higher internalizing and externalizing scores. Teachers' ratings of children at 11 years of age were associated with bone lead levels for a number of categories, including somatic complaints, anxious/depressed, social and attention problems, delinquent and aggressive behaviors, and internalizing and externalizing. Subjects with higher lead levels had higher scores in self-reports of delinquency at 11 years of age. Higher bone lead levels were associated with an increased risk of exceeding the clinical score for impaired attention, aggression, and delinquency, and these subjects were more likely to have worse scores on all items of the CBCL during the 4-year period of observation.

Consequences of Maternal Cigarette Smoking

A relatively large literature addresses the long-term consequences of maternal smoking during pregnancy in the offspring, which have revealed impairments after control of potential confounding variables. Maternal smoking during pregnancy results in decreased birth weight (*371,372*), which is itself a risk factor for later behavioral and other health problems. It is therefore not surprising that maternal smoking results in deficits in IQ in the offspring (*373,374*). Maternal smoking was also associated with increased aggressive behavior, as well as oppositional and overactive behavior in 1,377 twin pairs 3 years of age (*375*). Maternal cigarette smoking was associated with increased impulsivity (commission errors) on a continuous performance vigilance task in children 6 years of age (*376*). Fergusson et al. (*377*) observed a correlation between maternal cigarette smoking and an increased incidence of conduct disorders and depression in adolescents 16–18 years of age. Other studies have also found an association between antisocial behavior and maternal cigarette smoking in middle childhood (*378–380*) and adolescence (*381–383*). Finally, two recent studies identified a dose–effect relationship between maternal cigarette smoking and persistent criminal behavior. In one study (*384*), an increase in persistent criminal behavior was observed by 34 years of age in a cohort of 4,169 males, as ascertained from the Danish National Criminal Register, with effects observed with as few as 1–2 cigarettes per day smoked by the mother. In a similar study in Finland (*385*), a cohort of 5,636 males was followed prospectively from 6 months *in utero* to 28 years of age. Sons of mothers who smoked had a 2-fold (adjusted) increased risk for violent or repeated crimes but not nonviolent crimes. As pointed out by Fergusson (*386*), these effects of maternal cigarette smoking, observed in numerous studies, are resilient to control for confounding variables associated with cigarette smoking. However, it is interesting to note that in the Räsänen et al. (*385*) study, maternal smoking combined with risk factors including teenage pregnancy, single-parent family, and unwanted pregnancy increased the odds ratio 9-fold for violent crime and 14-fold for repeated crime.

Consequences of *in Utero* Exposure to Ethanol

In 1973 Jones and Smith (*387*) provided the first description in the English literature of a distinctive pattern of abnormalities in babies born to alcoholic mothers, which they named fetal alcohol syndrome (FAS). The faces of the children with FAS have a recognizable constellation of abnormalities, including short palpebral fissures, a flat midface, indistinct philtrum and thin upper lip, a low nasal bridge, short nose, micrognathia, and minor ear abnormalities, and often also include epicanthal folds (*388*). These children are also small for their age and may have limb and cardiac abnormalities. Individuals with FAS have severe dysmorphogenesis of the brain accompanied by characteristic behavioral problems, including lowered IQ and hyperactivity (*389*). A continuum of effects in humans is evident as a consequence of *in utero* alcohol exposure from relatively mild to severe, with individuals displaying varying degrees of the behavioral and physical anomalies associated with FAS. Children who have some but not all of the features of FAS are referred to as having fetal alcohol effects (FAE). These effects of prenatal exposure to ethanol have been replicated in animal models (*390*).

A longitudinal study on the effects of *in utero* exposure to alcohol has been ongoing in Seattle, Washington, since 1974–1975, at which time pregnant women were recruited into the study and questioned about their alcohol intake. Offspring of mothers consuming on average one drink per day exhibited neurological deficits as infants and deficits in memory, IQ, and school achievement, as well as attention deficits, increased impulsive behavior, and lack of cooperation (*391–393*). At 14 years of age, children in this cohort whose mothers drank an average of one drink per day during pregnancy still exhibited increased behavior/learning deficits (*394*). Individuals aged 16–27 with IQ scores in the normal range also exhibited impairment in tests of attention, memory, and executive function (*395*). Binge drinking (fewer than two drinks/occasion) by the mothers resulted in a profile of adolescent antisocial behavior (*394*).

The consequences of *in utero* exposure to alcohol are associated with other behaviors that make it difficult for an individual to integrate successfully into society. Further studies with persons with FAS/FAE identified a 50–60% incidence of mental health problems, trouble with the law, and inappropriate sexual behavior (*389,396*). In this group of adolescents, prenatal alcohol exposure was predictive of alcohol use, whereas living in an alcoholic family was not (*397*). In the Seattle cohort, 30 women with FAS/FAE had given birth to a child by 1997. Of these, 57% no longer had the child in their care, 40% drank during pregnancy, 17% had children with FAS/FAE, and an additional 13% had children with suspected FAS/FAE. These long-term effects of FAE represent a human tragedy of epic proportions, particularly because the estimate of full-blown FAS is 2.7–4.6 per 1,000 live births in the United States (*388*). The financial and social costs are enormous.

Monetary Consequences of a "Small" Effect on Cognition

"Small" functional effects often stimulate intense debate in the risk assessment community. A decrement in function that is still considered to be in the normal range may

ED_001854_00010737-00016

nonetheless have important consequences for a society, particularly if a large segment of the society is exposed. It is becoming increasingly well established that a common effect exposure to developmental neurotoxicants is a small decrement in IQ. The consequences of a shift in the IQ distribution have been discussed (*398,399*). Even a small shift to the left in the normal distribution has a large effect on the tails of the distribution. For example, a shift in the IQ of the population by 5 points results in a doubling of the number of individuals with IQs < 70 who would require greater educational resources in addition to other social supports. There would be a concomitant decrease in individuals with IQs > 130 by a factor of 2.5. There is also considerable evidence that there is a high correlation among IQ, education, and lifetime earnings. One of the most powerful and extensive databases is the government-funded National Longitudinal Survey of Youth (NLSY) (*400*), which has followed more than 12,000 young people from 3,000 households, now in their 30s, since 1979. Murray (*401*) used the NLSY database to calculate the consequences of childhood IQ to later earnings. He identified 710 sibling pairs in which one had a typical IQ (normal, 90–110) and one had an IQ either > 110 (bright) or < 90 (dull). He found that higher IQ was associated with higher incomes (Figure 17), more education, fewer total offspring, and

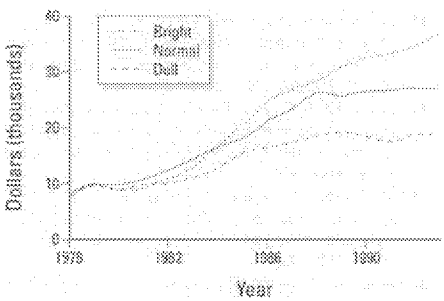


Figure 17. Earnings of paired siblings in which one sibling was labeled "normal" (IQ 90–110) and the other was either "bright" (IQ > 110) or "dull" (IQ < 90), based on the National Longitudinal Study of Youth (*400*). Adapted from Murray (*401*).

fewer offspring outside marriage. Whatever the cause of the IQ decrement (genetic and/or environmental, with exposure to a neurotoxic agent potentially contributing to both categories), the consequences have important implications for society.

The monetary cost associated with the ubiquitous exposure of fetuses and children to lead in industrialized societies has been calculated by Schwartz (*402*) in an estimation of the benefits of a 1-µg/dL reduction in the population mean blood lead concentration. The analysis was based on the monetary savings of reducing lead levels in children with blood lead concentrations between 10 and 20 µg/dL. Note that a 1-µg/dL reduction in blood lead concentrations would result in a shift in the population of < 1 IQ point based on meta-analyses (*403,404*). Schwartz (*402*) estimated medical costs associated with treatment of children with undue lead exposure, the increase in remedial education, and the costs associated with reduced birth weight and reduced gestational age, among other factors. The largest single cost was lost earnings as a result of decreased intellectual capability: $5.06 billion in 1994 dollars. The total cost, including increased medical care, compensatory education, and neonatal mortality and morbidity, was $6.94 billion 1994 dollars. In a later similar analysis using the NLSY database (*400*) to monetize the effect of decreased cognitive ability on earning capacity, the estimated gain in earnings was $7.5 billion U.S. per year for a decrease in blood lead levels of 1 µg/dL in the U.S. population (*405*). It is obvious that the small effect of lead on IQ is reflected in an enormous cost to society in lost potential and increased need for medical care and special education.

A similar analysis has been performed with respect to the societal cost of *in utero* exposure to cocaine (*406*). It is estimated that between 45,000 and 875,000 cocaine-exposed children are born in the United States each year. Lester et al. (*406*) performed a meta-analysis of studies of school-age children and calculated the effects of cocaine exposure on IQ and receptive and expressive language abilities (Table 2). The meta-analysis estimated a 3.26-point drop in IQ as a result of prenatal exposure, which would increase by 1.6 times the number of children with IQs < 70 (2 SDs below the mean IQ) for a cost of between $4 and 35 million dollars/year for special education, whereas children with an IQ of < 78 (1.5 SD below the mean) would cost between $10 and 80 million/year. The effect on language is even greater than that on IQ (as measured by effect size) and would result in additional total costs of $33–272 million/year. So, although the early concerns that cocaine-exposed babies would suffer from overt brain damage and intellectual impairment never materialized, the monetary cost of the more subtle impairment identified in these children is still enormous based on increased needs for educational intervention alone. Lester et al. (*406*) did not estimate costs of attentional, behavioral, or emotional problems, the cost of decreased earnings, or the possibility of antisocial behavior during adulthood.

Summary

It is important to reiterate that the nervous system develops over a very long period of time extending from the embryonic period through puberty, with both synaptogenesis and myelination continuing through puberty in both animals and humans. Even during adulthood there is continued recapitulation of synaptogenesis in the form of synaptic plasticity. This plasticity is modified by experience and environmental stimuli and continues to play a role in synaptic remodeling in both the developing and adult nervous system and is believed to underlie the efficacy and strength of synaptic transmission. Many agents can cause developmental neurotoxicity as a result of alterations in the developmental processes we have reviewed in this article. The actual mechanisms by which these processes are perturbed by vastly different chemical classes is an enigma and a continued research question. However, identification of perturbations of these developmental processes by xenobiotics and clinical disorders has led us to the recognition that a developmental insult can initiate

Table 2. Societal burden of prenatal cocaine exposure.

Measure	Effect (SE)	Percent < 2 SD (normal = 2.28%)	Increase	Additional affected children per year (*n*)	Additional cost for services (millions)	Percent < 1.5 SD (normal = 6.68%)	Increase	Additional affected children per year (*n*)	Additional cost for services (millions)
IQ difference	3.26 (2.01) IQ points	3.75	1.6 ×	1,688–14,062	$4–35	10.03	1.5 ×	4,514–37,612	$10–80
IQ effect size	0.33 (0.13) SD units	4.75	2.0 ×	2,138–17,812	$7–59	12.10	1.8 ×	5,445–45,375	$15–129
Receptive language effect size	0.71 (0.26) SD units	9.85	4.3 ×	4,432–36,938	$22–180	21.48	3.2 ×	9,666–80,550	$42–352
Expressive language effect size	0.60 (0.29) SD units	8.08	3.5 ×	3,636–30,300	$17–138	18.14	2.7 ×	8,163–68,025	$33–272

The calculations for children with IQs < 2 SD are included in the calculations for < 1.5 SD. Both calculations are provided because in some cases special education services are provided to children beginning at 1.5 SD below the mean (IQ < 78) and sometimes at 2 SD (IQ < 70). Adapted from Lester et al. (*406*).

ED_001854_00010737-00017

a cascade of alterations which may not be detected structurally or functionally until much later in life. Thus, these effects may be manifested at a time much removed from the critical developmental window when the exposure occurred. The developmental effects may be manifested as persistent deficits, developmental delays, or transient deficits. Developmental delays and transient deficits in these developmental processes and ontogeny of function may have more insidious consequences later in life. These two types of effects may result from the continued growth and differentiation of the nervous system resulting in apparent compensation. Such apparent recovery may be reversed during aging, when the compensatory ability of the nervous system may be significantly reduced. The critical nature of time of assessment for adverse effects after developmental perturbations may extend into aging because many structures of the brain (e.g., temporal lobe of the cerebral cortex) undergo age-related neuronal loss and concomitant loss of synaptic inputs and/or plasticity. In addition to latent neurotoxicity as a consequence of developmental exposure, there are tremendous impacts on society of small effects on function that may impair either cognitive or social performance (i.e., impulsivity, emotionality, and executive function) in individuals. The societal impact of these small or transient effects on the population can be tremendous when amortized across the population. These effects can result in an increased need for remedial assistance in school, increased medical care, increased assistance later in life with basic life skills, or increased mortality and morbidity during aging. These long-term consequences after developmental exposure to environmental agents require attention to the neurobiological substrates and processes that are homologous between animals and humans and which may be perturbed by environmental agents.

References and Notes

1. Atterberry TT, Burnett WT, Chambers JE. Age-related differences in parathion and chlorpyrifos toxicity in male rats: target and nontarget esterase sensitivity and cytochrome P450-mediated metabolism. Toxicol Appl Pharmacol 147:411–418 (1997).
2. Mortensen SR, Chanda SM, Hooper MJ, Padilla S. Maturational differences in chlorpyrifos-oxonase activity may contribute to age-related sensitivity to chlorpyrifos. J Biochem Toxicol 11:279–287 (1996).
3. Moser VC, Padilla S. Age- and gender-related differences in the time course of behavioral and biochemical effects produced by oral chlorpyrifos in rats. Toxicol Appl Pharmacol 149:107–119 (1998).
4. Moser VC, Chanda SM, Mortensen SR, Padilla S. Age- and gender-related differences in sensitivity to chlorpyrifos in the rat reflect developmental profiles of esterase activities. Toxicol Sci 46(2):211–222 (1999).
5. Chanda SM, Lassiter TL, Moser VC, Barone S Jr, Padilla S. Tissue carboxylesterase and chlorpyrifos toxicity in the developing rat. Hum Ecologic Risk Assess (in press).
6. Fechter LD. Distribution of manganese in development. Neurotoxicology 20:197–201 (1999).
7. Johnson GV, Watson AL Jr, Lartius R, Uemura E, Jope RS. Dietary aluminum selectively decreases MAP-2 in brains of developing and adult rats. Neurotoxicology 13:463–474 (1992).
8. Olson FC, Massaro EJ. Pharmacodynamics of placental transfer of methylmercury and induced teratology in mice. In: Trace Substances in Environmental Health IX (Hemphill DD, ed). Columbia, MO:University of Missouri,1975;403–408.
9. Null DH, Gartside PS, Wei E. Methylmercury accumulation in brains of pregnant, non-pregnant and fetal rats. Life Sci [II] 12:65–72 (1973).
10. Magos L. The absorption, distribution, and excretion of methyl mercury. In: The Toxicity of Methylmercury (Eccles CV, Annau Z, eds). Baltimore:Johns Hopkins University Press,1987;24–44.
11. Stanton ME, Crofton KM, Gray LE, Gordon CJ, Boyes WK, Mole ML, Peele DB, Bushnell PJ. Assessment of offspring development and behavior following gestational exposure to inhaled methanol in the rat. Fundam Appl Toxicol 28:100–110 (1995).
12. DeSesso JM. Comparative embryology. In: Handbook of Developmental Toxicology (Hood RD, ed). Boca Raton, FL:CRC Press, 1996;111–174.
13. Lewis DP, Van Dyke DC, Stumbo PJ, Berg MJ. Drug and environmental factors associated with adverse pregnancy outcomes. Part II: Improvement with folic acid. Ann Pharmacother 32:947–961 (1998).
14. Christensen B, Arbour L, Tran P, Leclerc D, Sabbaghian N, Platt R, Gilfix BM, Rosenblatt DS, Gravel RA, Forbes P, et al. Genetic polymorphisms in methylenetetrahydrofolate reductase and methionine synthase, folate levels in red blood cells, and risk of neural tube defects. Am J Med Genet 84:151–157 (1999).
15. Vorhees CV. Principles of behavioral teratology. In: Handbook of Behavioral Teratology (Riley EP, Vorhees CV, eds). New York:Plenum Press,1986;23–48.
16. Herschkowitz N, Kagan J, Zilles K. Neurobiological bases of behavioral development in the first year. Neuropediatrics 28:296–306 (1997).
17. Reznik BY, Minkov IP. The epidemiology of congenital abnormalities of the central nervous system in children. Neurosci Behav Physiol 23:94–96 (1993).
18. Roeleveld N, Zielhuis GA, Gabreels F. The prevalence of mental retardation: a critical review of recent literature. Dev Med Child Neurol 39:125–132 (1997).
19. Carpenter MB, Sutin J. Human Neuroanatomy. Baltimore: Williams & Wilkins, 1983;71–74.
20. Barone S Jr, Das KD, Lassiter TL, White LD. Vulnerable processes of nervous system development: a review of markers and methods. Neurotoxicology 21:15–36 (2000).
21. Koop M, Rilling G, Herrmann A, Kretschmann HJ. Volumetric development of the fetal telencephalon, cerebral cortex, diencephalon, and rhombencephalon including the cerebellum in man. Bibl Anat 28:53–78 (1986).
22. Bayer SA, Altman J, Russo RJ, Zhang X. Timetables of neurogenesis in the human brain based on experimentally determined patterns in the rat. Neurotoxicology 14:83–144 (1993).
23. Boulder Committee. Embryonic vertebrate central nervous system: revised terminology. Anat Rec 166:257–261 (1970).
24. Takahashi T, Nowakowski RS, Caviness VSJ. Early ontogeny of the secondary proliferative population of the embryonic murine cerebral wall. J Neurosci 15:6058–6068 (1995).
25. Bayer SA, Altman J. Neocortical Development. New York:Raven Press, 1991.
26. Rakic P, Caviness VSJ. Cortical development: view from neurological mutants two decades later. Neuron 14:1101–1104 (1995).
27. Bayer SA. Development of the hippocampal region in the rat. II: Morphogenesis during embryonic and early postnatal life. J Comp Neurol 190:115–134 (1980).
28. Jones EG, Valentino KL, Fleshman JWJ. Adjustment of connectivity in rat neocortex after prenatal destruction of precursor cells of layers II-IV. Brain Res 254:425–431 (1981).
29. Guerri C. Neuroanatomical and neurophysiological mechanisms involved in central nervous system dysfunctions induced by prenatal alcohol exposure. Alcohol Clin Exp Res 22:304–312 (1998).
30. Miller MW. Limited ethanol exposure selectively alters the proliferation of precursor cells in the cerebral cortex. Alcohol Clin Exp Res 20:139–143 (1996).
31. Whitney KD, Seidler FJ, Slotkin TA. Developmental neurotoxicity of chlorpyrifos: cellular mechanisms. Toxicol Appl Pharmacol 134:53–62 (1995).
32. Campbell CG, Seidler FJ, Slotkin TA. Chlorpyrifos interferes with cell development in rat brain regions. Brain Res Bull 43:179–189 (1997).
33. Roy TS, Andrews JE, Seidler FJ, Slotkin TA. Chlorpyrifos elicits mitotic abnormalities and apoptosis in neuroepithelium of cultured rat embryos. Teratology 58:62–68 (1998).
34. Song X, Violin JD, Seidler FJ, Slotkin TA. Modeling the developmental neurotoxicity of chlorpyrifos in vitro: macromolecule synthesis in PC12 cells. Toxicol Appl Pharmacol 151:182–191 (1998).
35. Rodier PM, Aschner M, Sager PR. Mitotic arrest in the developing CNS after prenatal exposure to methylmercury. Neurobehav Toxicol Teratol 6:379–385 (1984).
36. Ponce RA, Kavanagh TJ, Mottet NK, Whittaker SG, Faustman EM. Effects of methyl mercury on the cell cycle of primary rat CNS cells in vitro. Toxicol Appl Pharmacol 127:83–90 (1994).
37. Choi BH. The effects of methylmercury on the developing brain. Prog Neurobiol 32:447–470 (1989).
38. O'Rourke NA, Dailey ME, Smith SJ, McConnell SK. Diverse migratory pathways in the developing cerebral cortex. Science 258:299–302 (1992).
39. Marin-Padilla M. Early prenatal ontogenesis of the cerebral cortex (neocortex) of the cat (*Felis domestica*). A Golgi study. I: The primordial neocortical organization. Z Anat Entwicklungsgesch 134:117–145 (1971).
40. Angevine JB Jr, Sidman RL. Autoradiographic study of the cell migration during histogenesis of cerebral cortex in the mouse. Nature 192:766–768 (1961).
41. Ignacio MP, Kimm EJ, Kageyama GH, Yu J, Robertson RT. Postnatal migration of neurons and formation of laminae in rat cerebral cortex. Anat Embryol (Berl) 191:89–100 (1995).
42. Miller MW. Migration of cortical neurons is altered by gestational exposure to ethanol. Alcohol Clin Exp Res 17:304–314 (1993).
43. Choi BH, Lapham LW, Amin-Zaki L, Saleem T. Abnormal neuronal migration, deranged cerebral cortical organization, and diffuse white matter astrocytosis of human fetal brain: a major effect of methylmercury poisoning in utero. J Neuropathol Exp Neurol 37:719–733 (1978).
44. Choi BH. Methylmercury poisoning of the developing nervous system. I: Pattern of neuronal migration in the cerebral cortex. Neurotoxicology 7:591–600 (1986).
45. McConnell SK. The specification of neuronal identity in the mammalian cerebral cortex. Experientia 46:922–929 (1990).
46. Eagleson KL, Lillien L, Chan AV, Levitt P. Mechanisms specifying area fate in cortex include cell-cycle-dependent decisions and the capacity of progenitors to express phenotype memory. Development 124:1623–1630 (1997).
47. Geschwind N, Galaburda AM. Cerebral lateralization. Biological mechanisms, associations, and pathology. I: A hypothesis and a program for research. Arch Neurol 42:428–459 (1985).
48. Valles S, Sancho-Tello M, Minana R, Climent E, Renau-Piqueras J, Guerri C. Glial fibrillary acidic protein expression in rat brain and in radial glia culture is delayed by prenatal ethanol exposure. J Neurochem 67:2425–2433 (1996).
49. Valles S, Pitarch J, Renau-Piqueras J, Guerri C. Ethanol exposure affects glial fibrillary acidic protein gene expression and transcription during rat brain development. J Neurochem 69:2484–2493 (1997).
50. Laev H, Karpiak SE, Gokhale VS, Hungund BL. In utero ethanol exposure retards growth and alters morphology of cortical cultures: GM1 reverses effects. Alcohol Clin Exp Res 19:1226–1233 (1995).
51. Lauder JM, Schambra UB. Morphogenetic roles of acetylcholine. Environ Health Perspect 107(suppl 1):65–69 (1999).
52. Frischer RE, King JA, Rose KJ, Strand FL. Maturational changes in neonatal rat motor system with early postnatal administration of nicotine. Int J Dev Neurosci 6:149–154 (1988).
53. Slotkin TA, Lappi SE, Seidler FJ. Impact of fetal nicotine exposure on development of rat brain regions: critical sensitive periods or effects of withdrawal? Brain Res Bull 31:319–328 (1993).
54. Pennington SN, Sandstrom LP, Shibley IA Jr, Long SD, Beeker KR, Smith CP Jr, Lee K, Jones TA, Cummings KM, Means LW. Biochemical changes, early brain growth suppression and impaired detour learning in nicotine-treated chicks. Brain Res Dev Brain Res 83:181–189 (1994).
55. Cutler AR, Wilkerson AE, Gingras JL, Levin ED. Prenatal cocaine and/or nicotine exposure in rats: preliminary findings on long-term cognitive outcome and genital development at birth. Neurotoxicol Teratol 18:635–643 (1996).
56. Levitt P. Prenatal effects of drugs of abuse on brain development. Drug Alcohol Depend 51:109–125 (1998).
57. Audesirk T, Cabell L. Nanomolar concentrations of nicotine and cotinine alter the development of cultured hippocampal neurons via non-acetylcholine receptor-mediated mechanisms. Neurotoxicology 20:639–646 (1999).
58. Barone S Jr, Haykal-Coates N, Parran DK, Tilson HA. Gestational exposure to methylmercury alters the developmental pattern of trk-like immunoreactivity in the rat brain and results in cortical dysmorphology. Brain Res Dev Brain Res 109:13–31 (1998).

ED_001854_00010737-00018

59. Alfano DP, Petit TL. Neonatal lead exposure alters the dendritic development of hippocampal dentate granule cells. Exp Neurol 75:275–288 (1982).
60. Petit TL, LeBoutillier JC. Effects of lead exposure during development on neocortical dendritic and synaptic structure. Exp Neurol 64:482–492 (1979).
61. Petit TL, Alfano DP, LeBoutillier JC. Early lead exposure and the hippocampus: a review and recent advances. Neurotoxicology 4:79–94 (1983).
62. Norton S, Donoso JA. Forebrain damage following prenatal exposure to low-dose X-irradiation. Exp Neurol 87:185–197 (1985).
63. Sager PR, Aschner M, Rodier PM. Persistent, differential alterations in developing cerebellar cortex of male and female mice after methylmercury exposure. Brain Res 314:1–11 (1984).
64. Bailey CH, Chen M. Morphological aspects of synaptic plasticity in Aplysia. An anatomical substrate for long-term memory. Ann N Y Acad Sci 627:181–196 (1991).
65. Jacobson M. Formation of dendrites and development of synaptic connections. In: Developmental Neurobiology. New York:Plenum Press,1991;223–284.
66. Bourgeois JP, Goldman-Rakic PS, Rakic P. Synaptogenesis in the prefrontal cortex of rhesus monkeys. Cereb Cortex 4:78–96 (1994).
67. Uylings HB, van Eden CG. Qualitative and quantitative comparison of the prefrontal cortex in rat and in primates, including humans. Prog Brain Res 85:31–62 (1990).
68. Aghajanian GK, Bloom FE. The formation of synaptic junctions in developing rat brain: a quantitative electron microscopic study. Brain Res 6:716–727 (1967).
69. O'Callaghan JP. Assessment of neurotoxicity using assays of neuron- and glia-localized proteins: chronology and critique. In: Neurotoxicology (Tilson HA, Mitchell C, eds). New York:Raven Press, Ltd.,1992;83–99.
70. O'Callaghan JP, Miller DB. Assessment of chemically-induced alterations in brain development using assays of neuron- and glia-localized proteins. Neurotoxicology 10:393–406 (1989).
71. Elferink LA, Scheller RH. Synaptic vesicle proteins and regulated exocytosis. Prog Brain Res 105:79–85 (1995).
72. Represa A, Deloulme JC, Sensenbrenner M, Ben-Ari Y, Baudier J. Neurogranin: immunocytochemical localization of a brain-specific protein kinase C substrate. J Neurosci 10:3782–3792 (1990).
73. Barone S Jr, Stanton ME, Mundy WR. Neurotoxic effects of neonatal triethyltin (TET) exposure are exacerbated with aging. Neurobiol Aging 16:723–735 (1995).
74. Freeman JH Jr, Barone S Jr, Stanton ME. Disruption of cerebellar maturation by an antimitotic agent impairs the ontogeny of eyeblink conditioning in rats. J Neurosci 15:7301–7314 (1995).
75. Jones EG, Valentino KL, Fleshman JWJ. Adjustment of connectivity in rat neocortex after prenatal destruction of precursor cells of layers II-IV. Brain Res 254:425–431 (1981).
76. Sotelo C, Beaudet A. Influence of experimentally induced agranularity on the synaptogenesis of serotonin nerve terminals in rat cerebellar cortex. Proc R Soc Lond B Biol Sci 206:133–138 (1979).
77. Volk B. Cerebellar histogenesis and synaptic maturation following pre- and postnatal alcohol administration. An electron-microscopic investigation of the rat cerebellar cortex. Acta Neuropathol (Berl) 63:57–65 (1984).
78. Lancaster F, Delaney C, Samorajski T. Synaptic density of caudate-putamen and visual cortex following exposure to ethanol in utero. Int J Dev Neurosci 7:581–589 (1989).
79. Averill D, Needleman H. Neonatal lead exposure retards cortical synaptogenesis in the rat. In: Low Level Lead Exposure: The Clinical Implications of Current Research (Needleman H, ed). New York:Raven Press,1980;210.
80. McCauley PT, Bull RJ, Tonti AP, Lutkenhoff SD, Meister MV, Doerger JU, Stober JA. The effect of prenatal and postnatal lead exposure on neonatal synaptogenesis in rat cerebral cortex. J Toxicol Environ Health 10:639–651 (1982).
81. Hoff SF. Synaptogenesis in the hippocampal dentate gyrus: effects of in utero ethanol exposure. Brain Res Bull 21:47–54 (1988).
82. Kawamoto JC, Overmann SR, Woolley DE, Vijayan VK. Morphometric effects of preweaning lead exposure on the hippocampal formation of adult rats. Neurotoxicology 5:125–148 (1984).
83. Zanoli P, Truzzi C, Veneri C, Braghiroli D, Baraldi M. Methyl mercury during late gestation affects temporarily the development of cortical muscarinic receptors in rat offspring. Pharmacol Toxicol 75:261–264 (1994).
84. O'Callaghan JP, Miller DB. Acute exposure of the neonatal rat to triethyltin results in persistent changes in neurotypic and gliotypic proteins. J Pharmacol Exp Ther 244:368–378 (1988).
85. Mazer C, Muneyyirci J, Taheny K, Raio N, Borella A, Whitaker-Azmitia P. Serotonin depletion during synaptogenesis leads to decreased synaptic density and learning deficits in the adult rat: a possible model of neurodevelopmental disorders with cognitive deficits. Brain Res 760:68–73 (1997).
86. Veronesi B, Pope C. The neurotoxicity of parathion-induced acetylcholinesterase inhibition in neonatal rats. Neurotoxicology 11:465–482 (1990).
87. Eriksson P. Developmental neurotoxicity of environmental agents in the neonate. Neurotoxicology 18:719–726 (1997).
88. Penfield W. Cytology and Cellular Pathology of the Nervous System. New York:Paul B. Hoeber, Inc., 1932.
89. Watson WE. Physiology of neuroglia. Physiol Rev 54:245–271 (1974).
90. Thomas WE. Brain macrophages: evaluation of microglia and their functions. Brain Res Brain Res Rev 17:61–74 (1992).
91. Cuadros MA, Navascues J. The origin and differentiation of microglial cells during development. Prog Neurobiol 56:173–189 (1998).
92. Rakic P. Mode of cell migration to the superficial layers of fetal monkey neocortex. J Comp Neurol 145:61–83 (1972).
93. Soriano E, Alvarado-Mallart RM, Dumesnil N, del Rio JA, Sotelo C. Cajal-Retzius cells regulate the radial glia phenotype in the adult and developing cerebellum and alter granule cell migration. Neuron 18:563–577 (1997).
94. Wiggins RC. Myelination: a critical stage in development. Neurotoxicology 7(2):103–120 (1986).
95. Mission JP, Takahashi T, Caviness VSJ. Ontogeny of radial and other astroglial cells in murine cerebral cortex. Glia 4:138–148 (1991).
96. Streit WJ, Graeber MB, Kreutzberg GW. Functional plasticity of microglia: a review. Glia 1:301–307 (1988).
97. Norton WT, Aquino DA, Hozumi I, Chiu FC, Brosnan CF. Quantitative aspects of reactive gliosis: a review. Neurochem Res 17:877–885 (1992).
98. Price J. Glial cell lineage and development. Curr Opin Neurobiol 4:680–686 (1994).
99. Vernadakis A. Glia-neuron intercommunications and synaptic plasticity. Prog Neurobiol 49:185–214 (1996).
100. Miller RH, Ono K. Morphological analysis of the early stages of oligodendrocyte development in the vertebrate central nervous system. Microsc Res Tech 41:441–453 (1998).
101. Wiggins RC. Myelin development and nutritional insufficiency. Brain Res 257:151–175 (1982).
102. Iwasaki N, Hamano K, Okada Y, Horigome Y, Nakayama J, Takeya T, Takita H, Nose T. Volumetric quantification of brain development using MRI. Neuroradiology 39:841–846 (1997).
103. Hunter SF, Leavitt JA, Rodriguez M. Direct observation of myelination in vivo in the mature human central nervous system. A model for the behaviour of oligodendrocyte progenitors and their progeny. Brain 120(Pt 11):2071–2082 (1997).
104. Paus T, Zijdenbos A, Worsley K, Collins DL, Blumenthal J, Giedd JN, Rapoport JL, Evans AC. Structural maturation of neural pathways in children and adolescents: in vivo study. Science 283:1908–1911 (1999).
105. Lancaster FE, Mayur BK, Patsalos PN, Samorajski T, Wiggins RC. The synthesis of myelin and brain subcellular membrane proteins in the offspring of rats fed ethanol during pregnancy. Brain Res 235:105–113 (1982).
106. Riley EP, Mattson SN, Sowell ER, Jernigan TL, Sobel DF, Jones KL. Abnormalities of the corpus callosum in children prenatally exposed to alcohol. Alcohol Clin Exp Res 19:1198–1202 (1995).
107. Zoeller RT, Butnariu OV, Fletcher DL, Riley EP. Limited postnatal ethanol exposure permanently alters the expression of mRNAs encoding myelin basic protein and myelin-associated glycoprotein in cerebellum. Alcohol Clin Exp Res 18:909–916 (1994).
108. Harry GJ, Toews AD, Krigman MR, Morell P. The effect of lead toxicity and milk deprivation of myelination in the rat. Toxicol Appl Pharmacol 77:458–464 (1985).
109. Sundstrom R, Karlsson B. Myelin basic protein in brains of rats with low dose lead encephalopathy. Arch Toxicol 59:341–345 (1987).
110. Windebank AJ. Specific inhibition of myelination by lead in vitro; comparison with arsenic, thallium, and mercury. Exp Neurol 94:203–212 (1986).
111. Rothenberg SJ, Poblano A, Garza-Morales S. Prenatal and perinatal low level lead exposure alters brainstem auditory evoked responses in infants. Neurotoxicology 15:695–699 (1994).
112. Blaschke AJ, Staley K, Chun J. Widespread programmed cell death in proliferative and postmitotic regions of the fetal cerebral cortex. Development 122:1165–1174 (1996).
113. Blaschke AJ, Weiner JA, Chun J. Programmed cell death is a universal feature of embryonic and postnatal neuroproliferative regions throughout the central nervous system. J Comp Neurol 396:39–50 (1998).
114. Bredesen DE. Neural apoptosis. Ann Neurol 38:839–851 (1995).
115. Bursch W, Kleine L, Tenniswood M. The biochemistry of cell death by apoptosis. Biochem Cell Biol 68:1071–1074 (1990).
116. Raff MC, Barres BA, Burne JF, Coles HS, Ishizaki Y, Jacobson MD. Programmed cell death and the control of cell survival: lessons from the nervous system. Science 262:695–700 (1993).
117. White LD, Barone S Jr. Qualitatative and quantitative estimates of apoptosis from birth to senescence in the rat brain. Cell Death Differ (in press).
118. Simonati A, Rosso T, Rizzuto N. DNA fragmentation in normal development of the human central nervous system: a morphological study during corticogenesis. Neuropathol Appl Neurobiol 23:203–211 (1997).
119. Hoffman PL, Tabakoff B. To be or not to be: how ethanol can affect neuronal death during development. Alcohol Clin Exp Res 20:193–195 (1996).
120. Liesi P. Ethanol-exposed central neurons fail to migrate and undergo apoptosis. J Neurosci Res 48:439–448 (1997).
121. Fox DA, Campbell ML, Blocker YS. Functional alterations and apoptotic cell death in the retina following developmental or adult lead exposure. Neurotoxicology 18:645–664 (1997).
122. Oberto A, Marks N, Evans HL, Guidotti A. Lead (Pb^{+2}) promotes apoptosis in newborn rat cerebellar neurons: pathological implications. J Pharmacol Exp Ther 279:435–442 (1996).
123. Nagashima K. A review of experimental methylmercury toxicity in rats: neuropathology and evidence for apoptosis. Toxicol Pathol 25:624–631 (1997).
124. Busciglio J, Yankner BA. Apoptosis and increased generation of reactive oxygen species in Down's syndrome neurons in vitro. Nature 378:776–779 (1995).
125. Dragunow M, MacGibbon GA, Lawlor P, Butterworth N, Connor B, Henderson C, Walton M, Woodgate A, Hughes P, Faull RL. Apoptosis, neurotrophic factors and neurodegeneration. Rev Neurosci 8:223–265 (1997).
126. Barinaga M. Is apoptosis key in Alzheimer's disease? Science 281:1303–1304 (1998).
127. Butterworth NJ, Williams L, Bullock JY, Love DR, Faull RL, Dragunow M. Trinucleotide (CAG) repeat length is positively correlated with the degree of DNA fragmentation in Huntington's disease striatum. Neuroscience 87:49–53 (1998).
128. Burke RE, Kholodilov NG. Programmed cell death: does it play a role in Parkinson's disease? Ann Neurol 44:S126–S133 (1998).
129. Klein R. Role of neurotrophins in mouse neuronal development. FASEB J 8:738–744 (1994).
130. Zhou J, Bradford HF. Nerve growth factors and the control of neurotransmitter phenotype selection in the mammalian central nervous system. Prog Neurobiol 53:27–43 (1997).
131. Barone S Jr. Applications of the neurotrophic hypothesis to developmental neurotoxicology. In: Target Organ Toxicity-Neurotoxicology (Tilson HA, Harry GJ, eds). Washington, DC:Taylor & Francis,1999;179–200.
132. Zafra F, Hengerer B, Leibrock J, Thoenen H, Lindholm D. Activity dependent regulation of BDNF and NGF mRNAs in the rat hippocampus is mediated by non-NMDA glutamate receptors. EMBO J 9:3545–3550 (1990).
133. Patterson SL, Grover LM, Schwartzkroin PA, Bothwell M. Neurotrophin expression in rat hippocampal slices: a stimulus paradigm inducing LTP in CA1 evokes increases in BDNF and NT-3 mRNAs. Neuron 9:1081–1088 (1992).
134. Castrén E, da Penha B, Lindholm D, Thoenen H. Differential effects of MK-801 on brain-derived neurotrophic factor mRNA levels in different regions of the rat brain. Exp Neurol 122:244–252 (1993).
135. Bessho Y, Nakanishi S, Nawa H. Glutamate receptor agonists enhance the expression of BDNF mRNA in cultured cerebellar granule cells. Brain Res Mol Brain Res 18:201–208 (1993).
136. Wetmore C, Olson L, Bean AJ. Regulation of brain-derived neurotrophic factor (BDNF) expression and release from hippocampal neurons is mediated by non-NMDA type glutamate receptors. J Neurosci 14:1688–1700 (1994).
137. Lindholm D, Castren E, Berzaghi M, Blochl A, Thoenen H. Activity-dependent and hormonal regulation of neurotrophin mRNA levels in the brain—implications for neuronal plasticity. J Neurobiol 25:1362–1372 (1994).
138. Alberch J, Carman-Krzan M, Fabrazzo M, Wise BC. Chronic treatment with scopolamine and physostigmine changes nerve growth factor (NGF) receptor density and NGF content in rat brain. Brain Res 542:233–240 (1991).
139. Lindefors N, Ernfors P, Falkenberg T, Persson H. Septal cholinergic afferents regulate expression of brain-derived neurotrophic factor and beta-nerve growth factor mRNA in rat hippocampus. Exp Brain Res 88:78–90 (1992).

ED_001854_00010737-00019

140. Lapchak PA, Araujo DM, Hefti F. Cholinergic regulation of hippocampal brain-derived neurotrophic factor mRNA expression: evidence from lesion and chronic cholinergic drug treatment studies. Neuroscience 52:575–585 (1993).
141. da Penha B, Cooper J, Castrén E, Zafra F, Sofroniew M, Thoenen H, Lindholm D. Cholinergic regulation of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) but not neurotrophin-3 (NT-3) mRNA levels in the developing rat hippocampus. J Neurosci 13:3818–3826 (1993).
142. French SJ, Humby T, Horner CH, Sofroniew MV, Rattray M. Hippocampal neurotrophin and trk receptor mRNA levels are altered by local administration of nicotine, carbachol and pilocarpine. Brain Res Mol Brain Res 67:124–136 (1999).
143. Alberch J, Brito B, Notario V, Castro R. Prenatal haloperidol treatment decreases nerve growth factor receptor and mRNA in neonate rat forebrain. Neurosci Lett 131:228–232 (1991).
144. Zafra F, Castrén E, Thoenen H, Lindholm D. Interplay between glutamate and gamma-aminobutyric acid transmitter systems in the physiological regulation of brain-derived neurotrophic factor and nerve growth factor synthesis in hippocampal neurons. Proc Natl Acad Sci U S A 88:10037–10041 (1991).
145. Perez-Navarro E, Alberch J, Arenas E, Marsal J. Nerve growth factor and its receptor are differentially modified by chronic naltrexone treatment during rat brain development. Neurosci Lett 149:47–50 (1993).
146. Breese CR, D'Costa A, Ingram RL, Lenham J, Sonntag WE. Long-term suppression of insulin-like growth factor-1 in rats after in utero ethanol exposure: relationship to somatic growth. J Pharmacol Exp Ther 264:448–456 (1993).
147. Angelucci F, Cimino M, Balduini W, Piltillo L, Aloe L. Prenatal exposure to ethanol causes differential effects in nerve growth factor and its receptor in the basal forebrain of preweaning and adult rats. J Neural Transplant Plast 6:63–71 (1997).
148. Webb B, Suarez SS, Heaton MB, Walker DW. Cultured postnatal rat septohippocampal neurons change intracellular calcium in response to ethanol and nerve growth factor. Brain Res 778:354–366 (1997).
149. De Simone R, Aloe L. Influence of ethanol consumption on brain nerve growth factor and its target cells in developing and adult rodents. Ann Ist Super Sanita 29:179–183 (1993).
150. Dohrman DP, West JR, Pantazis NJ. Ethanol reduces expression of the nerve growth factor receptor, but not nerve growth factor protein levels in the neonatal rat cerebellum. Alcohol Clin Exp Res 21:882–893 (1997).
151. Rahman H, Kentroti S, Vernadakis A. Neuroblast cell death in ovo and in culture: interaction of ethanol and neurotrophic factors. Neurochem Res 19:1495–1502 (1994).
152. Angelucci F, Fiore M, Cozzari C, Aloe L. Prenatal ethanol effects on NGF level, NPY and ChAT immunoreactivity in mouse entorhinal cortex: a preliminary study. Neurotoxicol Teratol 21:415–425 (1999).
153. Haykal-Coates N, Shafer TJ, Mundy WR, Barone S Jr. Effects of gestational methylmercury exposure on immunoreactivity of specific isoforms of PKC and enzyme activity during post-natal development of the rat brain. Brain Res Dev Brain Res 109:33–49 (1998).
154. Mundy WR, Parran DK, Barone S Jr. Gestational exposure to methylmercury alters the developmental pattern of neurotrophin- and neurotransmitter-induced phosphoinositide (PI) hydrolysis. Neurotox Res 1(4):271–283 (2000).
155. Santucci D, Rankin J, Laviola G, Aloe L, Alleva E. Early exposure to aluminium affects eight-arm maze performance and hippocampal nerve growth factor levels in adult mice. Neurosci Lett 166:89–92 (1994).
156. Das KP, Lassiter TL, Lau C, Barone S Jr. Alterations of rat brain DNA and neurotrophin levels by prenatal exposure to chlorpyrifos. Toxicol Sci Suppl 48:186 (1999).
157. Eide FF, Lowenstein DH, Reichardt LF. Neurotrophins and their receptors—current concepts and implications for neurologic disease. Exp Neurol 121:200–214 (1993).
158. Buznikov GA, Shmukler Y, Lauder JM. Changes in the physiological roles of neurotransmitters during individual development. Neurosci Behav Physiol 29:11–21 (1999).
159. Cameron HA, Hazel TG, McKay RD. Regulation of neurogenesis by growth factors and neurotransmitters. J Neurobiol 36:287–306 (1998).
160. Chausovsky A, Tsarfaty I, Kam Z, Yarden Y, Geiger B, Bershadsky AD. Morphogenetic effects of neuregulin (neu differentiation factor) in cultured epithelial cells. Mol Biol Cell 9:3195–3209 (1998).
161. Bain G, Gottlieb DI. Neural cells derived by in vitro differentiation of P19 and embryonic stem cells. Perspect Dev Neurobiol 5:175–178 (1998).
162. Barker JL, Behar T, Li YX, Liu QY, Ma W, Maric D, Maric I, Schaffner AE, Serafini R, Smith SV, et al. GABAergic cells and signals in CNS development. Perspect Dev Neurobiol 5:305–322 (1998).
163. Gleason EL, Spitzer NC. AMPA and NMDA receptors expressed by differentiating *Xenopus* spinal neurons. J Neurophysiol 79:2986–2998 (1998).
164. Yeh GC, Hsieh TH, Chang SF. The negative influence of endogenous opioid receptor activity on the differentiation of the rat pheochromocytoma PC12 cells induced by nerve growth factor. Neurosci Lett 252:25–28 (1998).
165. Zagon IS, McLaughlin PJ. Naltrexone modulates body and brain development in rats: a role for endogenous opioid systems in growth. Life Sci 35:2057–2064 (1984).
166. Zagon IS, McLaughlin PJ. Increased brain size and cellular content in infant rats treated with an opiate antagonist. Science 221:1179–1180 (1983).
167. Schmahl W, Funk R, Miaskowski U, Plendl J. Long-lasting effects of naltrexone, an opioid receptor antagonist, on cell proliferation in developing rat forebrain. Brain Res 486:297–300 (1989).
168. Zagon IS, McLaughlin PJ. Endogenous opioid systems regulate cell proliferation in the developing rat brain. Brain Res 412:68–72 (1987).
169. Owen A, Bird M. Acetylcholine as a regulator of neurite outgrowth and motility in cultured embryonic mouse spinal cord. Neuroreport 6:2269–2272 (1995).
170. Sternfeld M, Ming G, Song H, Sela K, Timberg R, Poo M, Soreq H. Acetylcholinesterase enhances neurite growth and synapse development through alternative contributions of its hydrolytic capacity, core protein, and variable C termini. J Neurosci 18:1240–1249 (1998).
171. Grifman M, Galyam N, Seidman S, Soreq H. Functional redundancy of acetylcholinesterase and neuroligin in mammalian neuritogenesis. Proc Natl Acad Sci U S A 95:13935–13940 (1998).
172. Patel AJ, Barochovsky O, Lewis PD. Psychotropic drugs and brain development: effects on cell replication in vivo and in vitro. Neuropharmacology 20:1243–1249 (1981).
173. Lauder JM. Ontogeny of the serotonergic system in the rat: serotonin as a developmental signal. Ann N Y Acad Sci 600:297–313 (1990).
174. Lipton SA, Kater SB. Neurotransmitter regulation of neuronal outgrowth, plasticity and survival. Trends Neurosci 12:265–270 (1989).
175. Ben-Ari Y, Khazipov R, Leinekugel X, Caillard O, Gaiarsa JL. GABAA, NMDA and AMPA receptors: a developmentally regulated 'menage a trois.' Trends Neurosci 20:523–529 (1997).
176. Segovia S, del Cerro MC, Ortega E, Perez-Laso C, Rodriguez-Zafra C, Izquierdo MA, Guillamon A. Role of GABAA receptors in the organization of brain and behavioural sex differences. Neuroreport 7:2553–2557 (1996).
177. Liu J, Morrow AL, Devaud LL, Grayson DR, Lauder JM. Regulation of GABA(A) receptor subunit mRNA expression by the pesticide dieldrin in embryonic brainstem cultures: a quantitative, competitive reverse transcription-polymerase chain reaction study. J Neurosci Res 49:645–653 (1997).
178. Das KD, Chao S, White L, Haines W, Tilson HA, Harry GJ, Barone S Jr. Differential patterns of NGF, BDNF, and NT-3 mRNA and protein levels in developing cortical region of rat brain. Neuroscience (in press).
179. Furlong CE, Li WF, Costa LG, Richter RJ, Shih DM, Lusis AJ. Genetically determined susceptibility to organophosphorus insecticides and nerve agents: developing a mouse model for the human PON1 polymorphism. Neurotoxicology 19:645–650 (1998).
180. Li WF, Matthews C, Disteche CM, Costa LG, Furlong CE. Paraoxonase (PON1) gene in mice: sequencing, chromosomal localization and developmental expression. Pharmacogenetics 7:137–144 (1997).
181. Bourgeois JP, Rakic P. Changes of synaptic density in the primary visual cortex of the macaque monkey from fetal to adult stage. J Neurosci 13:2801–2820 (1993).
182. Rakic P, Bourgeois JP, Eckenhoff MF, Zecevic N, Goldman-Rakic PS. Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. Science 232:232–235 (1986).
183. Lidow MS, Goldman-Rakic PS, Rakic P. Synchronized overproduction of neurotransmitter receptors in diverse regions of the primate cerebral cortex. Proc Natl Acad Sci U S A 88:10218–10221 (1991).
184. Lidow MS, Rakic P. Scheduling of monoaminergic neurotransmitter receptor expression in the primate neocortex during postnatal development. Cereb Cortex 2:401–416 (1992).
185. Williams RW, Rakic P. Elimination of neurons from the rhesus monkey's lateral geniculate nucleus during development. J Comp Neurol 272:424–436 (1988).
186. Zecevic N, Bourgeois JP, Rakic P. Changes in synaptic density in motor cortex of rhesus monkey during fetal and postnatal life. Brain Res Dev Brain Res 50:11–32 (1989).
187. Zecevic N, Rakic P. Synaptogenesis in monkey somatosensory cortex. Cereb Cortex 1:510–523 (1991).
188. LaMantia AS, Rakic P. Axon overproduction and elimination in the corpus callosum of the developing rhesus monkey. J Neurosci 10:2156–2175 (1990).
189. Wiesel TN, Hubel DH. Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. J Neurophysiol 28:1029–1040 (1965).
190. Wiesel TN. Postnatal development of the visual cortex and the influence of environment. Nature 299:583–591 (1982).
191. Florence SL, Taub HB, Kaas JH. Large-scale sprouting of cortical connections after peripheral injury in adult macaque monkeys. Science 282:1117–1121 (1998).
192. Kaas JH, Florence SL, Jain N. Reorganization of sensory systems of primates after injury. Neuroscientist 3:123–130 (1997).
193. King AJ, Moore DR. Plasticity of auditory maps in the brain. Trends Neurosci 14:31–37 (1991).
194. Scheich H. Auditory cortex: comparative aspects of maps and plasticity. Curr Opin Neurobiol 1:236–247 (1991).
195. Rauschecker JP. Auditory cortical plasticity: a comparison with other sensory systems. Trends Neurosci 22:74–80 (1999).
196. Rauschecker JP. Developmental plasticity and memory. Behav Brain Res 66:7–12 (1995).
197. Diamond MC, Lindner B, Johnson R, Bennett EL, Rosenzweig MR. Differences in occipital cortical synapses from environmentally enriched, impoverished, and standard colony rats. J Neurosci Res 1:109–119 (1975).
198. Diamond MC, Ingham CA, Johnson RE, Bennett EL, Rosenzweig MR. Effects of environment on morphology of rat cerebral cortex and hippocampus. J Neurobiol 7:75–85 (1976).
199. Greenough WT, Volkmar FRR. Pattern of dendritic branching in occipital cortex of rats reared in complex environments. Exp Neurol 40:491–504 (1973).
200. Mollgaard K, Diamond MC, Bennett EL, Rosenzweig MR, Lindner B. Quantitative synaptic changes with differential experience in rat brain. Int J Neurosci 2:113–127 (1971).
201. Rosenzweig MR, Bennett EL. Psychobiology of plasticity: effects of training and experience on brain and behavior. Behav Brain Res 78:57–65 (1996).
202. Joseph R. Environmental influences on neural plasticity, the limbic system, emotional development and attachment: a review. Child Psychiatry Hum Dev 29:189–208 (1999).
203. Elbert T, Pantev C, Wienbruch C, Rockstroh B, Taub E. Increased cortical representation of the fingers of the left hand in string players. Science 270:305–307 (1995).
204. Jernigan TL, Trauner DA, Hesselink JR, Tallal PA. Maturation of human cerebrum observed in vivo during adolescence. Brain 114(Pt 5):2037–2049 (1991).
205. Steen RG, Ogg RJ, Reddick WE, Kingsley PB. Age-related changes in the pediatric brain: quantitative MR evidence of maturational changes during adolescence. Am J Neuroradiol 18:819–828 (1997).
206. Thompson PM, Giedd JN, Woods RP, MacDonald D, Evans AC, Toga AW. Growth patterns in the developing brain detected by using continuum mechanical tensor maps. Nature 404:190–193 (2000).
207. Prechtl HFR. The Neurological Examination of the Full-Term Newborn Infant. London:Heinemann, 1977.
208. Lester B. Data analysis and prediction. In: Neonatal Behavioral Assessment (Brazelton TB, eds). Philadelphia, PA: Lippincott,1984;85–96.
209. Honzik M. Value and limitations of infant tests: an overview. In: The Origins of Intelligence: Infancy and Early Childhood (Lewis M, ed). New York:Plenum Press,1976;59–95.
210. Rubin RA, Balow B. Measures of infant development and socioeconomic status as predictors of later intelligence and school achievement. Devel Psychol 15:225–227 (1979).
211. Largo RH, Howard JA. Developmental progression in play behavior of children between nine and thirty months. I: Spontaneous play and imitation. Dev Med Child Neurol 21:299–310 (1979).
212. Largo RH, Howard JA. Developmental progression in play behavior of children between nine and thirty months. II: Spontaneous play and language development. Dev Med Child Neurol 21:492–503 (1979).
213. Lyytinen P. Developmental trends in children's pretend play. Child Care Health Dev 17:9–25 (1991).
214. Russ SW. Play, creativity, and adaptive functioning: implications for play interventions. J Clin Child Psychol 27:469–480 (1998).
215. Ungerer JA, Sigman M. The relation of play and sensorimotor

ED_001854_00010737-00020

behavior to language in the second year. Child Dev 55:1448–1455 (1984).
216. Saunders I, Sayer M, Goodale A. The relationship between playfulness and coping in preschool children: a pilot study. Am J Occup Ther 53:221–226 (1999).
217. Fagan JF III. The paired-comparison paradigm and infant intelligence. Ann N Y Acad Sci 608:337–364 (1990).
218. Fagan JF III. Infant memory. History, current trends, relations to cognitive psychology. In: Infant Memory, Its Relation to Normal and Pathological Memory in Humans and Other Animals (Moscovitch M, ed). Mississauga, Ontario, Canada:Erindale College,1984;1–27.
219. Rose SA. Differential rates of visual information processing in full-term and preterm infants. Child Dev 54:1189–1198 (1983).
220. Gunderson VM, Grant-Webster KS, Sackett GP. Deficits in visual recognition in low birth weight infant pigtailed monkeys (*Macaca nemestrina*). Child Dev 60:119–127 (1989).
221. Gunderson VM, Grant KS, Burbacher TM, Fagan JF III, Mottet NK. The effect of low-level prenatal methylmercury exposure on visual recognition memory in infant crab-eating macaques. Child Dev 57:1076–1083 (1986).
222. Jacobson SW, Fein GG, Jacobson JL, Schwartz PM, Dowler JK. The effect of intrauterine PCB exposure on visual recognition memory. Child Dev 56:853–860 (1985).
223. Meltzoff AN. Towards a developmental cognitive science. The implications of cross-modal matching and imitation for the development of representation and memory in infancy. Ann N Y Acad Sci 608:1–31 (1990).
224. Rose SA, Feldman JF, Wallace IF. Infant information processing in relation to six-year cognitive outcomes. Child Dev 63:1126–1141 (1992).
225. Piaget J. The Construction of Reality in the Child. New York:Basic Books, 1954.
226. Burbacher TM, Grant KS, Mottet NK. Retarded object permanence development in methylmercury exposed *Macaca fascicularis* infants. Devel Psychol 22:771-776 (1986).
227. Paule MG, Chelonis JJ, Buffalo EA, Blake DJ, Casey PH. Operant test battery performance in children: correlation with IQ. Neurotoxicol Teratol 21:223–230 (1999).
228. Sen A, Jensen AR, Sen AK, Arora I. Correlation between reaction time and intelligence in psychometrically similar groups in America and India. Appl Res Ment Retard 4:139–152 (1983).
229. Jensen AR, Munro E. Reaction time, movement time, and intelligence. Intelligence 3:121–126 (1979).
230. Vernon PA. Speed of information processing and general intelligence. Intelligence 7:53–70 (1983).
231. Western SL, Long CJ. Relationship between reaction time and neuropsychological test performance. Arch Clin Neuropsychol 11:557–571 (1996).
232. Rice DC. Lack of effect of methylmercury exposure from birth to adulthood on information processing speed in the monkey. Neurotoxicol Teratol 20:275–283 (1998).
233. Adams J. Methods in behavioral teratology. In: Handbook of Behavioral Teratology (Riley EP, Vorhees CV, eds). New York:Plenum Press,1986;67–92.
234. U.S. Environmental Protection Agency. Testing guidelines; notice of availability. Fed Reg 61:8279-8282 (1996).
235. Bâ A, Seri BV. Psychomotor functions in developing rats: ontogenetic approach to structure-function relationships. Neurosci Biobehav Rev 19:413–425 (1995).
236. Altman J, Sudarshan K. Postnatal development of locomotion in the laboratory rat. Anim Behav 23:896–920 (1975).
237. Wier PJ, Guerriero FJ, Walker RF. Implementation of a primary screen for developmental neurotoxicity. Fundam Appl Toxicol 13:118–136 (1989).
238. Alder S, Zbinden G. Methods for the evaluation of physical, neuromuscular, and behavioral development of rats in early postnatal life. In: Methods in Prenatal Toxicology: Methods for the Evaluation of Physical, Neuromuscular, and Behavioral Development of Rats in Early Postnatal Life. Teratology Workshop, April 1977, Berlin (Neubert DM, Kwasigroch H-J, Alder TE, eds). Stuttgart:Thieme, 1977;175–185.
239. Bachevalier J, Beauregard M. Maturation of medial temporal lobe memory functions in rodents, monkeys, and humans. Hippocampus 3(spec no):191–201 (1993).
240. Winneke G, Brockhaus A, Baltissen R. Neurobehavioral and systemic effects of longterm blood lead-elevation in rats. I: Discrimination learning and open field-behavior. Arch Toxicol 37:247–263 (1977).
241. Rice DC. Behavioral effects of lead: commonalities between experimental and epidemiological data. Environ Health Perspect 104(suppl 2):337–351 (1996).
242. Evans HL, Daniel SA, Marmor M. Reversal learning tasks may provide rapid determination of cognitive deficits in lead-exposed children. Neurotoxicol Teratol 16:471–477 (1994).
243. Cory-Slechta DA, Pokora MJ, Widzowski DV. Behavioral manifestations of prolonged lead exposure initiated at different stages of the life cycle. II: Delayed spatial alternation. Neurotoxicology 12:761–776 (1991).
244. Rice DC, Gilbert SG. Lack of sensitive period for lead-induced behavioral impairment on a spatial delayed alternation task in monkeys. Toxicol Appl Pharmacol 103:364–373 (1990).
245. Rice DC, Karpinski KF. Lifetime low-level lead exposure produces deficits in delayed alternation in adult monkeys. Neurotoxicol Teratol 10:207–214 (1988).
246. Schantz SL, Moshtaghian J, Ness DK. Spatial learning deficits in adult rats exposed to *ortho*-substituted PCB congeners during gestation and lactation. Fundam Appl Toxicol 26:117–126 (1995).
247. Rice DC. Behavioral impairment produced by low-level postnatal PCB exposure in monkeys. Environ Res 80:S113–S121 (1999).
248. Webster MJ, Ungerleider LG, Bachevalier J. Development and plasticity of the neural circuitry underlying visual recognition memory. Can J Physiol Pharmacol 73:1364–1371 (1995).
249. Murray EA, Mishkin M. Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. J Neurosci 18:6568–6582 (1998).
250. Rice DC. Behavioral deficit (delayed matching to sample) in monkeys exposesd from birth to low levels of lead. Toxicol Appl Pharmacol 75:337–345 (1984).
251. Rice DC. Quantification of operant behavior. Toxicol Lett 43:361–379 (1988).
252. Cory-Slechta DA, Weiss B, Cox C. Delayed behavioral toxicity of lead with increasing exposure concentration. Toxicol Appl Pharmacol 71:342–352 (1983).
253. Rice DC. Effects of pre- plus postnatal exposure to methylmercury in the monkey on fixed interval and discrimination reversal performance. Neurotoxicology 13:443–452 (1992).
254. Rice DC, Gilbert SG, Willes RF. Neonatal low-level lead exposure in monkeys (*Macaca fascicularis*): locomotor activity, schedule-controlled behavior, and the effects of amphetamine. Toxicol Appl Pharmacol 51:503–513 (1979).
255. Gilbert SG, Rice DC, Burbacher TM. Fixed interval/fixed ratio performance in adult monkeys exposed in utero to methylmercury. Neurotoxicol Teratol 18:539–546 (1996).
256. Rice DC. Effect of postnatal exposure to a PCB mixture in monkeys on multiple fixed interval-fixed ratio performance. Neurotoxicol Teratol 19:429–434 (1997).
257. Lilienthal H, Neuf M, Munoz C, Winneke G. Behavioral effects of pre- and postnatal exposure to a mixture of low chlorinated PCBs in rats. Fundam Appl Toxicol 15:457–467 (1990).
258. Lilienthal H, Benthe C, Heinzow B, Winneke G. Impairment of schedule-controlled behavior by pre- and postnatal exposure to hexachlorobenzene in rats. Arch Toxicol 70:174–181 (1996).
259. Moser VC, Boyes WK, MacPhail RC. Investigations of amitraz neurotoxicity in rats. I: Effects on operant performance. Fundam Appl Toxicol 9:131–139 (1987).
260. Moser VC, MacPhail RC. Differential effects of formamidine pesticides on fixed-interval behavior in rats. Toxicol Appl Pharmacol 84:315–324 (1986).
261. Rice DC. Effects of postnatal exposure of monkeys to a PCB mixture on spatial discrimination reversal and DRL performance. Neurotoxicol Teratol 20:391–400 (1998).
262. Strupp BJ, Bunsey M, Levitsky DA, Hamberger K. Deficient cumulative learning: an animal model of retarded cognitive development. Neurotoxicol Teratol 16:71–79 (1994).
263. Campione JC, Brown AL. Learning ability and transfer propensity as sources of individual differences in intelligence. In: Learning and Cognition in the Mentally Retarded (Brooks PH, Sperber RD, McCauley C, eds). Baltimore, MD:University Press,1984;265–294.
264. Rice DC. Developmental lead exposure: neurobehavioral consequences. In: Handbook of Developmental Neurotoxicology (Slikker WJ, Chang LW, eds). San Diego, CA:Academic Press,1998;539–557.
265. Koopman-Esseboom C, Weisglas-Kuperus N, de Ridder MA, van der Paauw CG, Tuinstra LG, Sauer PJ. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. Pediatrics 97:700–706 (1996).
266. Patandin S, Lanting CI, Mulder PG, Boersma ER, Sauer PJ, Weisglas-Kuperus N. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. J Pediatr 134:33–41 (1999).
267. Boyes WK. Rat and human sensory evoked potentials and the predictability of human neurotoxicity from rat data. Neurotoxicology 15:569–578 (1994).
268. Murata K, Weihe P, Renzoni A, Debes F, Vasconcelos R, Zino F, Araki S, Jorgensen PJ, White RF, Grandjean P. Delayed evoked potentials in children exposed to methylmercury from seafood. Neurotoxicol Teratol 21:343–348 (1999).
269. Murata K, Weihe P, Araki S, Budtz-Jorgensen E, Grandjean P. Evoked potentials in Faroese children prenatally exposed to methylmercury. Neurotoxicol Teratol 21:471–472 (1999).
270. Otto D, Baumann SB, Robinson GS, Schroeder SR, Kleinbaum DG, Barton CN, Mushak D. Auditory and visual evoked potentials in children with undue lead absorption [Abstract]. Toxicology 5:81 (1985).
271. Goldey ES, Kehn LS, Lau C, Rehnberg GL, Crofton KM. Developmental exposure to polychlorinated biphenyls (Aroclor 1254) reduces circulating thyroid hormone concentrations and causes hearing deficits in rats. Toxicol Appl Pharmacol 135:77–88 (1995).
272. Lebel J, Mergler D, Lucotte M, Amorim M, Dolbec J, Miranda D, Arantes G, Rheault I, Pichet P. Evidence of early nervous system dysfunction in Amazonian populations exposed to low levels of methylmercury. Neurotoxicology 17:157–167 (1996).
273. Dahl R, White RF, Weihe P, Sorensen N, Letz R, Hudnell HK, Otto DA, Grandjean P. Feasibility and validity of three computer-assisted neurobehavioral tests in 7-year-old children. Neurotoxicol Teratol 18:413–419 (1996).
274. Fox DA. Psychophysically and electrophysiologically determined spatial deficits in developmentally lead-exposed rats have a cholinergic component. In: Cellular and Molecular Neurotoxicology (Narahashi T, ed). New York:Raven Press,1984;123–140.
275. Rice DC. Effects of lifetime lead exposure on spatial and temporal visual function in monkeys. Neurotoxicology 19:893–902 (1998).
276. Steckler T, Inglis W, Winn P, Sahgal A. The pedunculopontine tegmental nucleus: a role in cognitive processes? Brain Res Rev 19:298–318 (1994).
277. Montague PR, Dayan P, Sejnowski TJ. A framework for mesencephalic dopamine systems based on predictive Hebbian learning. J Neurosci 16:1936–1947 (1996).
278. Thach WT. A role for the cerebellum in learning movement coordination. Neurobiol Learn Mem 70:177–188 (1998).
279. Parkins EJ. Cerebellum and cerebrum in adaptive control and recognition: a review. Biol Cybern 77:79–87 (1997).
280. Petrosini L, Leggio MG, Molinari M. The cerebellum in the spatial problem solving: a co-star or a guest star? Prog Neurobiol 56:191–210 (1998).
281. Mishkin M, Appenzeller T. The anatomy of memory. Sci Am 256:80–89 (1987).
282. Murray E. What have ablation studies told us about the neural substrates of stimulus memory? Sem Neurosci 8:13–22 (1996).
283. Wise SP, Murray EA, Gerfen CR. The frontal cortex-basal ganglia system in primates. Crit Rev Neurobiol 10:317–356 (1996).
284. Murray E. Memory systems in the primate brain. Sem Neurosci 8:1–2 (1996).
285. Zola-Morgan S, Squire LR. The components of the medial temporal lobe memory system. In: Neuropsychology of Memory (Squire LR, Butters N, eds). New York:Guilford Press, 1992;325–335.
286. Zola-Morgan S, Squire LR. Medial temporal lesions in monkeys impair memory on a variety of tasks sensitive to human amnesia. Behav Neurosci 99:22–34 (1985).
287. Alvarez P, Zola-Morgan S, Squire LR. Damage limited to the hippocampal region produces long-lasting memory impairment in monkeys. J Neurosci 15:3796–3807 (1995).
288. Alvarez P, Zola-Morgan S, Squire LR. The animal model of human amnesia: long-term memory impaired and short- term memory intact. Proc Natl Acad Sci U S A 91:5637–5641 (1994).
289. Kolb B, Tees RC. The Cerebral Cortex of the Rat. Cambridge, MA:The MIT Press, 1990.
290. Heimer L. The Human Brain and Spinal Cord. New York:Springer-Verlag, 1983.
291. Uhlrich DJ, Essock EA, Lehmkuhle S. Cross-species correspondence of spatial contrast sensitivity functions. Behav Brain Res 2:291–299 (1981).
292. Uylings HBM, van Eden CG. Qualitative and quantitative comparision of the prefrontal cortex in rat and in primates, including humans. In: The Prefrontal Cortex-Its Structure, Function and Pathology (Uylings HBM, van Eden CG, de Bruin JPC, Corner MA, Feenstra MGP, eds). Amsterdam:Elsevier,1990;31–62.
293. Fuster JM. The Prefrontal Cortex. New York:Raven Press, 1989.
294. Uylings HBM, van Eden CG, de Bruin JPC, Corner MA, Feenstra MG. The Prefrontal Cortex-Its Structure, Function and Pathology. Amsterdam:Elsevier, 1990.
295. Smith EE, Jonides J. Storage and executive processes in the frontal lobes. Science 283:1657–1661 (1999).

ED_001854_00010737-00021

296. Robbins TW. Dissociating executive functions of the prefrontal cortex. Philos Trans R Soc Lond B Biol Sci 351:1463–1470 (1996).
297. Gold PW. Lack of attention from loss of time. Science 281:1149–1150 (1998).
298. Rice DC. Anatomical substrates of behavioral impairment induced by developmental lead exposure in monkeys: Inferences from brain lesions. Am Zool 37:409–425 (1997).
299. Eichenbaum H, Clegg RA, Feeley A. Reexamination of functional subdivisions of the rodent prefrontal cortex. Exp Neurol 79:434–451 (1983).
300. Fuster JM. Prefrontal cortex and the bridging of temporal gaps in the perception-action cycle. Ann N Y Acad Sci 608:318–329 (1990).
301. Diamond A. Evidence for the importance of dopamine for prefrontal cortex functions early in life. Philos Trans R Soc Lond B Biol Sci 351:1483–1493 (1996).
302. Goldman-Rakic PS. Development of cortical circuitry and cognitive function. Child Dev 58:601–622 (1987).
303. Diamond A, Goldman-Rakic PS. Comparison of human infants and rhesus monkeys on Piaget's AB task: evidence for dependence on dorsolateral prefrontal cortex. Exp Brain Res 74:24–40 (1989).
304. Bachevalier J, Mishkin M. An early and a late developing system for learning and retention in infant monkeys. Behav Neurosci 98:770–778 (1984).
305. Overman WH, Bachevalier J, Turner M, Peuster A. Object recognition versus object discrimination: comparison between human infants and infant monkeys. Behav Neurosci 106:15–29 (1992).
306. Zola-Morgan S, Squire LR. The neuropsychology of memory. Parallel findings in humans and nonhuman primates. Ann N Y Acad Sci 608:434–450 (1990).
307. Bachevalier J. Ontogenetic development of habit and memory formation in primates. Ann N Y Acad Sci 608:457–477 (1990).
308. Diamond A. Rate of maturation of the hippocampus and the developmental progression of children's performance on the delayed non-matching to sample and visual paired comparison tasks. Ann N Y Acad Sci 608:394–426 (1990).
309. Bachevalier J, Brickson M, Hagger C. Limbic-dependent recognition memory in monkeys develops early in infancy. Neuroreport 4:77–80 (1993).
310. Beauregard M, Malkova L, Bachevalier J. Stereotypies and loss of social affiliation after early hippocampectomy in primates. Neuroreport 6:2521–2526 (1995).
311. Bachevalier J, Hagger C, Bercu B. Gender differences in visual habit formation in 3-month-old rhesus monkeys. Dev Psychobiol 22:585–599 (1989).
312. Overman WH, Bachevalier J, Schuhmann E, Ryan P. Cognitive gender differences in very young children parallel biologically based cognitive gender differences in monkeys. Behav Neurosci 110:673–684 (1996).
313. Clark AS, Goldman-Rakic PS. Gonadal hormones influence the emergence of cortical function in nonhuman primates. Behav Neurosci 103:1287–1295 (1989).
314. Silva PA, McGee R, Williams S. A longitudinal study of the intelligence and behavior of preterm and small for gestational age children. J Dev Behav Pediat 5:1–5 (1984).
315. Pryor J, Silva PA, Brooke M. Growth, development and behaviour in adolescents born small-for-gestational-age. J Paediatr Child Health 31:403–407 (1995).
316. Siegel LS. Correction for prematurity and its consequences for the assessment of the very low birth weight infant. Child Dev 54:1176–1188 (1983).
317. Hultman CM, Sparen P, Takei N, Murray RM, Cnattingius S. Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: case-control study. Br Med J 318:421–426 (1999).
318. Hultman CM, Ohman A, Cnattingius S, Wieselgren IM, Lindstrom LH. Prenatal and neonatal risk factors for schizophrenia. Br J Psychiatry 170:128–133 (1997).
319. Wright P, Takei N, Rifkin L, Murray RM. Maternal influenza, obstetric complications, and schizophrenia. Am J Psychiatry 152:1714–1720 (1995).
320. Frangou S, Murray RM. Imaging as a tool in exploring the neurodevelopment and genetics of schizophrenia. Br Med Bull 52:587–596 (1996).
321. Rakic P, Bourgeois JP, Goldman-Rakic PS. Synaptic development of the cerebral cortex: implications for learning, memory, and mental illness. Prog Brain Res 102:227–243 (1994).
322. Williamson P, Drost D, Stanley J, Carr T, Morrison S, Merskey H. Localized phosphorus 31 magnetic resonance spectroscopy in chronic schizophrenic patients and normal controls. Arch Gen Psychiatry 48:578 (1991).
323. Selemon LD, Rajkowska G, Goldman-Rakic PS. Abnormally high neuronal density in the schizophrenic cortex. A morphometric analysis of prefrontal area 9 and occipital area 17. Arch Gen Psychiatry 52:805–818 (1995).
324. Beckmann H, Lauer M. The human striatum in schizophrenia. II: Increased number of striatal neurons in schizophrenics. Psychiatry Res 68:99–109 (1997).
325. Shenton ME, Kikinis R, Jolesz FA, Pollak SD, LeMay M, Wible CG, Hokama H, Martin J, Metcalf D, Coleman M. Abnormalities of the left temporal lobe and thought disorder in schizophrenia. A quantitative magnetic resonance imaging study. N Engl J Med 327:604–612 (1992).
326. Nopoulos P, Torres I, Flaum M, Andreasen NC, Ehrhardt JC, Yuh WT. Brain morphology in first-episode schizophrenia. Am J Psychiatry 152:1721–1723 (1995).
327. Rapoport JL, Giedd J, Kumra S, Jacobsen L, Smith A, Lee P, Nelson J, Hamburger S. Childhood-onset schizophrenia. Progressive ventricular change during adolescence. Arch Gen Psychiatry 54:897–903 (1997).
328. Goldman-Rakic PS, Selemon LD. Functional and anatomical aspects of prefrontal pathology in schizophrenia. Schizophr Bull 23:437–458 (1997).
329. Bertolino A, Knable MB, Saunders RC, Callicott JH, Kolachana B, Mattay VS, Bachevalier J, Frank JA, Egan M, Weinberger DR. The relationship between dorsolateral prefrontal *N*-acetylaspartate measures and striatal dopamine activity in schizophrenia. Biol Psychiatry 45:660–667 (1999).
330. Beauregard M, Bachevalier J. Neonatal insult to the hippocampal region and schizophrenia: a review and a putative animal model. Can J Psychiatry 41:446–456 (1996).
331. Galaburda AM, Sherman GF, Rosen GD, Aboitiz F, Geschwind N. Developmental dyslexia: four consecutive patients with cortical anomalies. Ann Neurol 18:222–233 (1985).
332. Galaburda AM, Kemper TL. Cytoarchitectonic abnormalities in developmental dyslexia: a case study. Ann Neurol 6:94–100 (1979).
333. Geschwind N, Galaburda AM. Cerebral lateralization. Biological mechanisms, associations, and pathology. I: A hypothesis and a program for research. Arch Neurol 42:428–459 (1985).
334. Denenberg VH, Mobraaten LE, Sherman GF, Morrison L, Schrott LM, Waters NS, Rosen GD, Behan PO, Galaburda AM. Effects of the autoimmune uterine/maternal environment upon cortical ectopias, behavior and autoimmunity. Brain Res 563:114–122 (1991).
335. Denenberg VH, Sherman GF, Schrott LM, Rosen GD, Galaburda AM. Spatial learning, discrimination learning, paw preference and neocortical ectopias in two autoimmune strains of mice. Brain Res 562:98–104 (1991).
336. Boehm GW, Sherman GF, Hoplight BJ, Hyde LA, Waters NS, Bradway DM, Galaburda AM, Denenberg VH. Learning and memory in the autoimmune BXSB mouse: effects of neocortical ectopias and environmental enrichment. Brain Res 726:11–22 (1996).
337. Annegers JF, Rocca WA, Hauser WA. Causes of epilepsy: contributions of the Rochester epidemiology project. Mayo Clin Proc 71:570–575 (1996).
338. Paneth N. The causes of cerebral palsy. Recent evidence. Clin Invest Med 16:95–102 (1993).
339. Barcovitch AJ, Truwit CC. Brain damage from perinatal asphyxia: correlation of MR findings with gestational age. Am J Neuroradiol 11:1087–1096 (1990).
340. Krageloh-Mann I, Hagberg B, Petersen D, Riethmuller J, Gut E, Michaelis R. Bilateral spastic cerebral palsy—pathogenetic aspects from MRI. Neuropediatrics 23:46–48 (1992).
341. Bryson SE, Clark BS, Smith IM. First report of a Canadian epidemiological study of autistic syndromes. J Child Psychol Psychiatry 29:433–445 (1988).
342. Strömland K, Nordin V, Miller M, Akerstrom B, Gillberg C. Autism in thalidomide embryopathy: a population study. Dev Med Child Neurol 36:351–356 (1994).
343. Rodier PM, Ingram JL, Tisdale B, Croog VJ. Linking etiologies in humans and animal models: studies of autism. Reprod Toxicol 11:417–422 (1997).
344. Carpenter EM, Goddard JM, Chisaka O, Manley NR, Capecchi MR. Loss of Hox-A1 (Hox-1.6) function results in the reorganization of the murine hindbrain. Development 118:1063–1075 (1993).
345. Gavalas A, Studer M, Lumsden A, Rijli FM, Krumlauf R, Chambon P. Hoxa1 and Hoxb1 synergize in patterning the hindbrain, cranial nerves and second pharyngeal arch. Development 125:1123–1136 (1998).
346. Helmbacher F, Pujades C, Desmarquet C, Frain M, Rijli FM, Chambon P, Charnay P. Hoxa1 and Krox-20 synergize to control the development of rhombomere 3. Development 125:4739–4748 (1998).
347. Hong YS, Kim SY, Bhattacharya A, Pratt DR, Hong WK, Tainsky MA. Structure and function of the HOX A1 human homeobox gene cDNA. Gene 159:209–214 (1995).
348. Weiss B, Simon W. Quantitative perspectives on the long-term toxicity of methylmercury and similar poisons. In: Behavioral Toxicology (Weiss B, Simon W, eds). New York:Plenum Press,1975;429–438.
349. Office of Technology Assessment. Neurotoxicity: Identifying and Controlling Poisons of the Nervous System. Washington, DC:U.S. Government Printing Office, 1990.
350. Weiss B. Risk assessment: the insidious nature of neurotoxicity and the aging brain. Neurotoxicology 11:305–313 (1990).
351. Wallace RB, Daniels CE, Altman J. Behavioral effects of neonatal irradiation of the cerebellum. 3: Qualitative observations in aged rats. Dev Psychobiol 5:35–41 (1972).
352. Spyker JM. Behavioral teratology and toxicology. In: Behavioral Toxicology (Weiss B, Laties VG, eds). New York:Plenum Press,1975;311–344.
353. Rice DC. Evidence for delayed neurotoxicity produced by methylmercury. Neurotoxicology 17:583–596 (1996).
354. Igata A, Niina K, Hamada R, Ohkatsu Y. The late onset of organic mercury intoxication after exposure. In: Studies on the Health Effects of Alkylmercury in Japan. Tokyo:Environment Agency, Japan, 1975;178–181.
355. Tsubaki T, Irukayama K. Minamata Disease. Amsterdam: Elsevier, 1977.
356. Kinjo Y, Higashi H, Nakano A, Sakamoto M, Sakai R. Profile of subjective complaints and activities of daily living among current patients with Minamata disease after 3 decades. Environ Res 63:241–251 (1993).
357. Rice DC. Delayed neurotoxicity in monkeys exposed developmentally to methylmercury. Neurotoxicology 10:645–650 (1989).
358. Rice DC, Gilbert SG. Effects of developmental methylmercury exposure or lifetime lead exposure on vibration sensitivity function in monkeys. Toxicol Appl Pharmacol 134:161–169 (1995).
359. Rice DC. Age-related increase in auditory impairment in monkeys exposed in utero plus postnatally to methylmercury. Toxicol Sci 44:191–196 (1998).
360. Rice DC, Hayward S. Comparison of visual function at adulthood and during aging in monkeys exposed to lead or methylmercury. Neurotoxicology 20(5):767–784 (1999).
361. Martyn CN, Barker DJ, Osmond C. Motoneuron disease and past poliomyelitis in England and Wales. Lancet 1:1319–1322 (1988).
362. Giancola PR, Zeichner A. Neuropsychological performance on tests of frontal lobe functioning and aggressive behavior in males. J Abnorm Psychol 103:832–835 (1994).
363. Goodman R. The relationship between normal variation in IQ and common childhood psychopathology: a clinical study. Eur Child Adolesc Psychiat 4:187–196 (1995).
364. Seguin JR, Pihl RO, Harden PW, Tremblay RE, Boulerice B. Cognitive and neuropsychological characteristics of physically aggressive boys. J Abnorm Psychol 104:614–624 (1995).
365. Lambert NM. Adolescent outcomes for hyperactive children. Perspectives on general and specific patterns of childhood risk for adolescent educational, social, and mental health problems. Am Psychol 43:786–799 (1988).
366. Tiihonen J, Isohanni M, Rasanen P, Koiranen M, Moring J. Specific major mental disorders and criminality: a 26-year prospective study of the 1966 northern Finland birth cohort. Am J Psychiatry 154:840–845 (1997).
367. Sciarillo WG, Alexander G, Farrell KP. Lead exposure and child behavior. Am J Public Health 82:1356–1360 (1992).
368. Wasserman GA, Staghezza-Jaramillo B, Shrout P, Popovac D, Graziano J. The effect of lead exposure on behavior problems in preschool children. Am J Public Health 88:481–486 (1998).
369. Bellinger D, Leviton A, Allred E, Rabinowitz M. Pre- and postnatal lead exposure and behavior problems in school-aged children. Environ Res 66:12–30 (1994).
370. Needleman HL, Riess JA, Tobin MJ, Biesecker GE, Greenhouse JB. Bone lead levels and delinquent behavior. JAMA 275:363–369 (1996).
371. Kramer MS. Intrauterine growth and gestational duration determinants. Pediatrics 80:502–511 (1987).
372. English PB, Eskenazi B. Reinterpreting the effects of maternal smoking on infant birthweight and perinatal mortality: a multivariate approach to birthweight standardization. Int J Epidemiol 21:1097–1105 (1992).
373. Fried P, Watkinson B, Gray R. Differential effects on cognitive functioning in 9- to 12-year-olds exposed to cigarettes and marihuana. Neurotoxicol Teratol 20:293–306 (1998).
374. Naeye RL, Peters EC. Mental development of children whose mothers smoked during pregnancy. Obstet Gynecol 64:601–607 (1984).

ED_001854_00010737-00022

375. Orlebeke JF, Knol DL, Verhulst FC. Increase in child behavior problems resulting from maternal smoking during pregnancy. Arch Environ Health 52:317–321 (1997).
376. Leech SL, Richardson GA, Goldschmidt L, Day NL. Prenatal substance exposure: effects on attention and impulsivity of 6-year-olds. Neurotoxicol Teratol 21:109–118 (1999).
377. Fergusson DM, Woodward LJ, Horwood LJ. Maternal smoking during pregnancy and psychiatric adjustment in late adolescence. Arch Gen Psychiatry 55:721–727 (1998).
378. Weitzman M, Gortmaker S, Sobol A. Maternal smoking and behavior problems of children. Pediatrics 90:342–349 (1992).
379. Fergusson DM, Horwood LJ, Lynskey MT. Maternal smoking before and after pregnancy: effects on behavioral outcomes in middle childhood. Pediatrics 92:815–822 (1993).
380. Milberger S, Biederman J, Faraone SV, Chen L, Jones J. Is maternal smoking during pregnancy a risk factor for attention deficit hyperactivity disorder in children? Am J Psychiatry 153:1138–1142 (1996).
381. Rantakallio P. A follow-up study up to the age of 14 of children whose mothers smoked during pregnancy. Acta Paediatr Scand 72:747–753 (1983).
382. Rantakallio P, Laara E, Isohanni M, Moilanen I. Maternal smoking during pregnancy and delinquency of the offspring: an association without causation? Int J Epidemiol 21:1106–1113 (1992).
383. Wakschlag LS, Lahey BB, Loeber R, Green SM, Gordon RA, Leventhal BL. Maternal smoking during pregnancy and the risk of conduct disorder in boys. Arch Gen Psychiatry 54:670–676 (1997).
384. Brennan PA, Grekin ER, Mednick SA. Maternal smoking during pregnancy and adult male criminal outcomes. Arch Gen Psychiatry 56:215–219 (1999).
385. Räsänen P, Hakko H, Isohanni M, Hodgins S, Järvelin MR, Tiihonen J. Maternal smoking during pregnancy and risk of criminal behavior among adult male offspring in the Northern Finland 1966 Birth Cohort. Am J Psychiatry 156:857–862 (1999).
386. Fergusson DM. Prenatal smoking and antisocial behavior. Arch Gen Psychiatry 56:223–224 (1999).
387. Jones KL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. Lancet 2:999–1001 (1973).
388. Sampson PD, Streissguth AP, Bookstein FL, Little RE, Clarren SK, Dehaene P, Hanson JW, Graham JM, Jr. Incidence of fetal alcohol syndrome and prevalence of alcohol-related neurodevelopmental disorder. Teratology 56:317–326 (1997).
389. Streissguth AP, Kanter J. The Challenge of Fetal Alcohol Syndrome: Overcoming Secondary Disabilities. Seattle, WA:University of Washington Press, 1997.
390. Maier SE, Miller JA, West JR. Prenatal binge-like alcohol exposure in the rat results in region- specific deficits in brain growth. Neurotoxicol Teratol 21:285–291 (1999).
391. Streissguth AP, Bookstein KL, Sampson PD, Barr HM. The Enduring Effects of Prenatal Alcohol Exposure on Child Development: Birth through 7 Years, A Partial Least Squares Solution. Ann Arbor, MI:University of Michigan Press, 1993.
392. Streissguth AP, Barr HM, Olson HC, Sampson PD, Bookstein FL, Burgess DM. Drinking during pregnancy decreases word attack and arithmetic scores on standardized tests: adolescent data from a population-based prospective study. Alcohol Clin Exp Res 18:248–254 (1994).
393. Streissguth AP, Sampson PD, Olson HC, Bookstein FL, Barr HM, Scott M, Feldman J, Mirsky AF. Maternal drinking during pregnancy: attention and short-term memory in 14-year-old offspring—a longitudinal prospective study. Alcohol Clin Exp Res 18:202–218 (1994).
394. Olson HC, Streissguth AP, Sampson PD, Barr HM, Bookstein FL, Thiede K. Association of prenatal alcohol exposure with behavioral and learning problems in early adolescence. J Am Acad Child Adolesc Psychiatry 36:1187–1194 (1997).
395. Kerns KA, Don A, Mateer CA, Streissguth AP. Cognitive deficits in nonretarded adults with fetal alcohol syndrome. J Learn Disabil 30:685–693 (1997).
396. Famy C, Streissguth AP, Unis AS. Mental illness in adults with fetal alcohol syndrome or fetal alcohol effects. Am J Psychiatry 155:552–554 (1998).
397. Baer JS, Barr HM, Bookstein FL, Sampson PD, Streissguth AP. Prenatal alcohol exposure and family history of alcoholism in the etiology of adolescent alcohol problems. J Stud Alcohol 59:533–543 (1998).
398. Weiss JL, Schell RE. Estimating WAIS-R IQ from the Shipley Institute of Living Scale: a replication. J Clin Psychol 47:558–562 (1991).
399. Rice DC. Issues in developmental neurotoxicology: interpretation and implications of the data. Can J Public Health 89(suppl 1):S31–S40 (1998).
400. National Longitudinal Surveys. Available: http://www.bls.gov/nlshome.htm [cited 11 May 2000].
401. Murray C. The Bell Curve. Quoted in Holden C. Random samples. Science 276:1651 (1997).
402. Schwartz J. Low-level lead exposure and children's IQ: a meta-analysis and search for a threshold. Environ Res 65:42–55 (1994).
403. Schwartz J. Societal benefits of reducing lead exposure. Environ Res 66:105–124 (1994).
404. International Programme on Chemical Safety. Environmental Health Criteria 165: Inorganic Lead. Geneva:World Health Organization, 1995.
405. Salkever DS. Updated estimates of earnings benefits from reduced exposure of children to environmental lead. Environ Res 70:1–6 (1995).
406. Lester BM, LaGasse LL, Seifer R. Cocaine exposure and children: the meaning of subtle effects. Science 282:633–634 (1998).

ED_001854_00010737-00023

Western Journal of Nursing Research, 2004, 26(2), 146-166

Hispanic Adolescent Farmworkers' Perceptions Associated With Pesticide Exposure[1]

Mary K. Salazar
Marie Napolitano
Jennifer A. Scherer
Linda A. McCauley

The migrant farmworker population in the United States is a vulnerable and understudied population whose characteristics are constantly shifting. The number of youth involved in agriculture work is increasing, and they, in particular, may be at increased risk for occupational hazards, such as pesticide exposure. The present study utilized an ecological framework for focus group discussions with 33 adolescent migrant farmworkers in Oregon. Adolescents' risk perception and health beliefs associated with pesticide exposure are examined on four levels of environmental influence: microenvironment, organizational environment, social/community environment, and macroenvironment. Adolescents provided insight on such topics as perceived vulnerability of illness due to pesticide exposure, attitudes toward farmwork, influence of their boss, knowledge of occupational hazards, safety training, and barriers to occupational choice. Cultural influences on occupational safety and health are discussed and increased attention to safety training is recommended.

Keywords: *farmworker; pesticide; agriculture; risk perception; occupational hazard; ecological model; adolescent*

Agricultural work is one of the most dangerous occupations in the United States. In addition to suffering a disproportionate rate of occupational fatalities and high rates of disabling injuries (National Safety Council, 2002),

Mary K. Salazar, Ed.D., R.N., COHN-S, Professor and Director, Occupational Health Nursing Program, School of Nursing, University of Washington, Seattle, Washington; *Marie Napolitano,* Ph.D., R.N., Associate Professor, School of Nursing, Oregon Health & Science University; *Jennifer A. Scherer,* M.P.H., Senior Research Assistant, Center for Research on Occupational and Environmental Toxicology, Oregon Health & Science University; *Linda A. McCauley,* Ph.D., R.N., FAAN, Professor and Scientist, Center for Research on Occupational and Environmental Toxicology, Oregon Health & Science University, Portland, Oregon.

DOI: 10.1177/0193945903259579
© 2004 Sage Publications

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

ED_001854_00010738-00001

farmworkers are regularly exposed to toxic chemicals designed to kill living organisms. Although the targets of these chemicals are insects, fungi, rodents, and other organisms that interfere with crop production, they can also have detrimental effects on human health (Arcury, Quandt, & Russell, 2002). Acute effects of pesticide exposures include headaches, nausea, eye irritation, skin rashes, and flu-like symptoms. Long-term effects include neurological and reproductive disorders, such as fetal deaths and deformities, liver and kidney disease, as well as various forms of cancer (Davis, 1997; U.S. General Accounting Office [GAO], 2000).

There are approximately 2.5 million seasonal and migrant farmworkers in the United States; approximately 1.8 million work with crops and thus are potentially exposed to pesticides (U.S. GAO, 2000). The extent of pesticide-related illness among these workers is unknown. Although 10,000 to 20,000 incidents of physician-diagnosed cases are reported each year, this number may represent "serious underreporting" (U.S. GAO, 2000). In fact, the U.S. Environmental Protection Agency (EPA) suspects that as many as 300,000 farmworkers suffer from pesticide-related illness each year, and that many of these are children (Davis, 1997). According to Fleming and Herzstein (1997), minority and disadvantaged persons, such as migrant farmworkers, are particularly vulnerable to pesticide health effects. They are likely to have higher home and environmental exposures and are also more likely to have occupational exposures.

In 1992, the EPA revised the Worker Protection Standard so that it would more effectively protect agricultural workers from pesticide exposure. The standard prohibits pesticide spraying when anyone is in the fields, and it restricts treated areas for specified periods of time. It also requires employers to provide workers with pesticide safety training and decontamination supplies (i.e., soap, water, towels) and that workers receive information about when and where pesticides have been applied. The standard applies to all agricultural workers who perform tasks related to the cultivation and harvesting of plants, including children who work in the fields (EPA, 1999; U.S. GAO, 2000).

YOUTH WORKING IN AGRICULTURE

Although the number of farmworker youths is not reliably known, estimates suggest that approximately 7% of seasonal and migrant farmworkers are between the ages of 14 and 17 (Acosta & Lee, 2001). Because these youths are smaller and are still developing, they are particularly vulnerable

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

to the adverse effects of pesticide exposure (Davis, 1997; U.S. GAO, 2000). The adequacy of agricultural safety and health training and the effectiveness of protective standards for youth workers have been questioned (Quandt, Arcury, Austin, & Cabrera, 2001; Shu et al., 1988); furthermore, the practices and training designed for adults may not be adequate for an adolescent population (Committee on the Health and Safety Implications of Child Labor, 1998; McCauley, Sticker, Bryan, Lasarev, & Scherer, 2002). Documented insights into the work lives of migrant adolescent farmworkers as a group are limited; accounts of their work experiences are embedded in the sparse information on farmworkers in general, and much of that information focuses on inter- and intrapersonal influences on occupational health and safety. Few studies examine the multitude of social, organizational, and other external environments that have the potential to affect the health and safety of these young workers. There is a critical need to understand the unique work experiences and perceptions of the migrant youths and to identify the full range of factors that affect their ability to protect themselves from workplace hazards.

PURPOSE AND AIMS

The purpose of this descriptive study was to elicit migrant adolescent farmworkers' perceptions about pesticide exposures. To capture the full spectrum of factors, an ecological approach was used to guide the collection of data. Ecological theory offers a convenient means to scrutinize the context of human experiences (Bronfenbrenner, 1977). A distinctive feature of an ecological approach is that it does not limit an investigation to personal influences on behaviors (beliefs, knowledge, and attitudes); rather, it provides a means to examine complex interrelationships that occur between humans and their environments (Linnan, Sorenson, Colditz, Klar, & Emmons, 2001; Newes-Adeyi, Helitzer, Caulfield, & Bronner, 2000; Richard, Potvin, Kishchuk, Prlic, & Green, 1996). An underlying premise of this theory is that improving health and safety is not just a matter of changing the behaviors of individuals; rather, to be effective, programs must consider and target the multiple influences on behaviors.

An ecological framework typically consists of multiple nested levels of interacting and interconnected systems. For the purposes of the present study, four levels of influence were considered: the microenvironment (immediate surroundings of the worker), the organizational environment (structures and functions that characterize the work organization), the social/

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

community environment (interrelationships and interaction among various systems in which the organization is embedded), and the macroenvironment (larger context that contains all other levels of the system). The aims of the study were to examine the adolescents' microenvironment, including their personal attributes that may affect pesticide exposure; to identify organizational variables in terms of their influence on exposure occurrence; to describe social and cultural systems that affect the lives and work of these adolescents; and to examine the macroenvironement, including the values, traditions, rules, and regulations that may influence pesticide exposure.

Focus Groups

Because of the paucity of information specific to the adolescent experience with pesticides and the meaning of agricultural work, an exploratory approach using focus sessions was used for the present study. Focus groups have been successfully used as a research strategy with various cultural groups (Anderson, Goddard, Garcia, Guzman, & Vasquez, 1998; Bauer, Rodriquez, Quiroga, & Flores-Ortiz, 2000; Groff et al., 2000; Lalonde, Rabinowitz, Sherfsky, & Washienko, 1997; Williams, Abbott, & Taylor, 1997) including Latino farmworkers (Napolitano & Beltran, 1998; Napolitano et al., 2002; Perilla, Wilson, Wold, & Spencer, 1998; Wilson, Pittman, & Wold, 2000). A key advantage of this technique is that the opinions of several participants can be obtained in a single session. Focus sessions assume the importance of the participants' viewpoints as the meanings of a phenomenon are explored (Benoliel, 1984; Marshall & Rossman, 1989). The group experience can help overcome a reluctance to speak to someone perceived as more powerful and to overcome the limitations imposed by low literacy skills or limited experience thinking and speaking about certain issues. Disadvantages include possible bias or 'group think' responses. Comments may be influenced by the way the questions are asked or how the moderator responds. The potential for socially desirable responses may be especially pronounced because the respondents may attempt to please not only the moderator but also other session participants.

SAMPLE

The study participants consisted of adolescents ranging from ages 11 to 18 years who maintained a migrant lifestyle and who either worked or were planning to work in agriculture. Participants were recruited from a state

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

TABLE 1: Background Information of Focus Group Participants

	Region A		*Region B*	*Region C*		
	Group 1	*Group 2*	*Group 3*	*Group 4*	*Group 5*	*Total*
N	6	8	5	6	8	33
Males (*n*)	2	3	2	5	7	19
Age (mean years)	13.2	15.0	14.2	16.3	17.2	15.2
Self-reported language proficiency (*n*)						
English	6	8	5	0	3	22
Spanish	6	8	5	6	8	33
Indigenous dialect	1	0	1	4	6	12
Any formal U.S. education[a]	6	8	5	1	3	23

a. Enrollment in regular school year as opposed to only English as a Second Language courses.

Migrant Education Program (MEP), an evening English as a Second Language (ESL) program, or from migrant farmworker housing camps. All participants received pesticide training, as required by the EPA (1990) Worker Protection Act. The training, which was provided by EPA-certified trainers, consisted of a video or flip-chart presentation that described hazards related to pesticide exposure and methods that could be used to reduce risks. The focus sessions occurred approximately 2 weeks following the training. Recruitment was conducted face-to-face by project staff until the desired number of participants was attained. To reduce the tendency for group fragmentation, groups were limited to 6 to 10 adolescents (Krueger, 1994; Morgan, 1998).

Description of the Sample

The mean age of the 33 adolescents recruited for the study was 15.2 ($SD \pm 2.1$) with the majority between the ages of 13 and 16 years (Table 1). Nineteen were young men; 14 were young women. All participants were of Hispanic origin; 59.4% were born in Latin America (18 in Mexico, 1 in Guatemala), and 40.6% were born in the United States. Of the participants, 23 (71.9%) had some formal education in the United States; the remaining 28.1% received their education in Mexico. The two predominant languages were English and Spanish; 100% of the participants spoke Spanish, 68.8% spoke English, and 37.5% spoke an indigenous dialect.

During the focus groups, participants were asked to indicate their age when they began working in the fields. Of the 22 who responded, 90%

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

indicated that they were younger than the age of 13 years when they began working. The average age was 10.9 years; however, four participants indicated that they were 8 years of age. The majority (89.3%) performed fieldwork, such as harvesting and related activities, whereas 10.7% performed other tasks, such as keeping the field clean or picking rocks. Fieldwork consisted of hoeing, planting, pruning, as well as picking crops and loading containers. Some stated that they lifted and carried these containers as well. Other types of work reported included cutting grass and packing crops (on a packaging line). Two participants indicated that they occasionally mix or apply pesticides.

METHOD

Data Collection and Analysis

The number of groups needed for focus sessions partially depends on the diversity of the participants. Studies using this technique typically include from three to six sessions (Ludwig-Beymer, Blankemeier, Casas-Byots, & Suarez-Balcazar, 1996; Maynard-Tucker, 2000; Owen, 2001). For the purposes of the present study, five focus sessions were conducted with groups of adolescent migrant farmworkers who were located in three separate regions of Oregon (Table 1). All procedures used in the present study were approved by the Institutional Review Board of Oregon Health & Science University. Prior to data collection, the researchers obtained informed written consent directly from the participants, in keeping with the approved human participants application. A $5 incentive was offered to compensate the adolescents for their time and effort.

The moderator for the groups was a 23-year-old bilingual/bicultural Hispanic man with extensive experience working with youths, as well as experience working in the agriculture industry. The primary role of the moderator was to establish rapport with the group, ask the interview questions, and keep the discussion focused. The moderator was trained in fundamentals of focus group facilitation, and one pilot session was conducted. An additional research member served as an observer at each group. The primary role of the observer was to assist with the facilitation of the sessions as needed, to oversee the audiotaping, to take field notes, and to respond to questions per the moderator or participant's request. The semistructured interview guide based on the ecological model developed for the present study consisted of questions and probes that were sequenced to capture views through a natural

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

and logical flow of discussion (Krueger, 1994). For example, participants were asked to describe their perceptions about hazards related to pesticides; they were then asked to describe their personal experiences with pesticides.

Each group determined its language of choice. At the request of participants, 3 of the 5 sessions were conducted primarily in English with some Spanish; two sessions were conducted entirely in Spanish. The sessions were 60 min to 80 min in length. On completion of the focus sessions, the Spanish audiotapes were translated into English, and all sessions were transcribed. Group facilitators and project staff reviewed the transcriptions for accuracy. Three members of the research team reviewed each transcript word by word, line by line. Constant comparative analysis was used to identify codes and categorize the predominant themes. After the first three focus sessions, the identified findings and themes were used to generate a list of follow-up questions to facilitate more information in the final two sessions. This process was intended to ensure as far as possible that an exhaustive list of themes was obtained.

FINDINGS

Application of the Ecological Model

The analysis resulted in the identification of a taxonomy of themes that were ultimately categorized under the four ecological levels of influence developed for the present study.

Microenvironment

The microenvironment reflects those surroundings that are closest to the lives of these young workers and includes their day-to-day activities and interactions with family, friends, and coworkers. Analysis of the focus group discussions revealed multiple influences on the adolescents' attitudes about work-related hazards, including perceived vulnerability, attitudes about hazards, and attitudes about work (see Table 2 for categories of responses).

Perceived vulnerability. Concerns about personal vulnerability to pesticides were related to the participants' knowledge and beliefs about occupational disease. Some identified specific diseases that could be related to occupational exposure to pesticides, whereas others described disease outcomes

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

TABLE 2: Categories of Responses

- Microenvironment
  - Perceived vulnerability
  - Protective behaviors
  - Attitudes about agricultural work
- Organization environment
  - Structural influences
    - Dealing with the "boss"
    - The physical environment
  - Functions influencing health and safety
    - Health and safety training
- Social/community environment
  - Learning about fieldwork
  - Knowledge about hazards
  - Managing work and school
- Macroenvironment
  - Barriers to choice
  - Traditional values
  - Rules and regulations

NOTE: Although the ecological approach provides a useful organizational framework and a systematic and structured way to examine complex phenomena, a high degree of interaction and interrelationship exists between the various levels of the model. In view of this, discrete categorization may not be appropriate for certain factors, and some factors may appear at more than one level.

in more generic terms. Specific diseases mentioned included cancer, skin disorders such as "bumps" and "rashes," high fever, asthma, and other allergic reactions. Perceptions of the relationship between certain kinds of exposures and the occurrence of cancer are reflected by this statement:

> Some chemicals are found to be leading to cancer. You can get skin cancer if you have a lot of sunlight exposure, and if you get pesticides on your skin, and if it is not washed right away, I suppose you can get cancer.

One adolescent did not mention any specific conditions but stated that "something serious can happen" when one works in the fields and related this "serious" occurrence to the person's overall status: "If someone is weak, it affects him or her quickly, and little by little, they get sick." One youth indicated that it was important to protect himself because "You are still growing, and you don't have much tolerance to many things." Two participants noted that pesticides were especially dangerous to pregnant women. Consistent in all the focus sessions was the suggestion that getting sick was an inevitable part of the job: "Everybody knows you are going to get sick someway. You are going to get a headache from the sun, or you are going to get sunburn or whatever."

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

Protective behaviors. Although participants indicated that they recognized the importance of protective behaviors, complying with recommendations was another matter, as illustrated by one youth who stated that he recognized that pesticides were around when he ate his lunch, however, "You are like so hungry; you sit down wherever you can . . . sometimes you don't even wash your hands." Participants suggested that failure to wash was a result of time constraints, lack of education about hazards, and in some instances, complacency. "When you go to lunch, you don't have time to wash your hands," stated one youth. Another suggested that "Most people don't have the education or experience [to know about the hazards]. They don't know what's going to hurt them." Participants also stated that they would continue to eat contaminated berries out of the fields without washing them, because "Sometimes we don't care, we are used to it." And besides "It looks clean!" and "It looks delicious!" (For more detailed examples of responses, see the appendix.)

Although some youths stated they would refuse to work in an unsafe environment, others stated that it depended on the benefit derived. As stated by one, "Pay me enough money, then I will do it." Another youth stated that getting sick "is the risk you're willing to take to get money." One group had a discussion regarding the difference in attitudes about contaminants at work compared to other environments. When working in the field, "I don't really care, because when you are in the field, you are all dirty; it is okay if the food is all dirty too." On the other hand, "In your house, if the tortilla falls on the ground, you throw it away because there is more. In the field, it means I am out of food so I just keep it."

Participants also indicated that it was not always easy to wear protective clothing (identified as long-sleeved shirts, pants, hat, bandanas, and thick socks). As an example, a participant stated that he would wear protective clothing when he went into the field; however, when he got hot, he would find it intolerable: "In the morning you . . . are dressed like you are going to ski; by the end of the day, it looks like you are going swimming." Another youth candidly stated that he knows he should keep his protective clothing on, "But knowing me, I would probably change into some shorts and a tank top" if it was hot. It is also difficult to wear respiratory protection, even a simple cloth over one's mouth. As stated by one participant, "We don't cover our mouths because it's hard to breathe."

Attitudes about agricultural work. Adolescent farmworkers displayed a wide range of positive and negative opinions about the meaning and value of work in their lives. The positive aspects of fieldwork included working with one's friends and family and working outdoors. Although many viewed the

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

job as "very hard work," they also perceived it as an opportunity to learn "a lot of things you didn't know." One adolescent stated that he worked "because we need to get ahead, and one needs to be prepared for everything."

The financial rewards of working were perceived in varying ways. In every session, at least some of the youths indicated that they used their earnings to assist their families in some form or another, and several indicated that they had a responsibility to financially contribute to their families: "[I work in order to] help [my] parents with things they don't have." One youth stated that it was the custom for parents to take their children to work at a young age because they need to help their families financially. A youth from Mexico stated that he liked to work because it enabled him to help his parents; and another indicated that he sent most of his money to Mexico. A few youths stated they liked to make money so they could go shopping and "buy things," such as clothing.

Although many adolescents described positive aspects of working, negative themes emerged as well. The physical labor associated with this work was viewed as demanding and arduous. "It is a very hard job," said one. "You get dirty, and then you sweat, and then you get tired," stated another. "You get dirt in your shoes and you feel yuk." Dealing with the weather conditions also affected attitudes about work, and some workers described how weather had the potential to increase worker risk. It often rains when the workers are in the fields, stated one youth, and the ground becomes slippery, leading to a risk for injury. Other days were windy "and you breathe in this dust and everything." Electrical storms, yet another weather hazard, were noted by another participant.

Organizational Environment

The structure and functions of an organization are important determinants of worker health in any setting. The structure includes the management, the rules and regulations, and the physical characteristics of the work setting. The function refers to how the work is done. Functions aimed at protecting workers include health and safety training and education.

Structural Influences

Dealing with the "boss". Participants identified an array of people who they perceived as their "bosses" including the farm owner, crew boss, and field boss. Participants typically had some level of contact with the boss. Although some youths described their bosses as "pretty good," others

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

described them as uncaring: "Some bosses don't care about the workers, they just care about the work to be done. They just care about the money." And another: "They worry about the fruit a lot. They don't worry about the people." In a more dramatic response, one youth stated, "A person could die, and it wouldn't affect [the bosses] at all because there are more people that can do [the work]." When asked how he would react if the boss asked him to do something that may be dangerous at work, another youth responded, "The bosses say they are the ones in charge and that we either take the job or leave it." Participants stated that workers were fearful of the boss, afraid that the boss would get angry at them: "It was all about not to get the boss mad. Don't get fired!" One participant stated that he would not leave his place in the field to wash his hands because "the boss would see you leave and get mad."

Attitude about the physical environment. There was a range of opinions about the health and safety effects of the physical environment in this work setting. Participants provided several examples of deficiencies, such as lack of availability of soap and water: We "need more water faucet things where people can wash hands . . . so many workers and not enough water for everyone to wash hands and to drink . . . so people can protect themselves." Oftentimes, workers will bring bottled water because of concerns about water contamination. "At some point, irrigation water gets in contact with sewage and chemicals and that's not good." Other supplies are also not available. For example, one worker, when describing a lack of toilet paper, stated, "They may stock one day and then it runs out and they don't put anymore." Although the provision of protective clothing, such as long rubber boots, rubber jackets, and pants, was viewed as the responsibility of the boss, with one exception, workers indicated that they provided their own protective garments.

Functions Influencing Health and Safety

Health and safety training. Health and safety training may or may not be provided by the employer. When it was provided, it was not always well understood; as stated by one youth, "Sometimes the boss is talking so fast and using these big words, and I don't understand, and I am just staring at him." In some cases, others said information is provided in English to workers who do not speak English. Although some bosses were described as "good in that they teach you how to use the tools," one youth suggested that others "don't want to waste their time" telling workers about health and safety issues. In some cases, the perceived degree of hazard also seemed to determine whether safety information was provided by the boss. When describing the informa-

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

tion he received about tractor hazards, one youth stated, "He would teach me precautions for big things, but not . . . for pesticides. I guess pesticides was a small thing." Some participants believed that their immigrant status (lack of documentation) placed them in a powerless position. Because they were perceived as powerless, the boss may feel less compelled to provide pesticide education. In some cases, fear impeded the worker's ability to get desired information. Participants indicated that they would not ask questions regarding pesticides, and they would not ask for clarification if work-related instructions were not understood.

Social/Community Environment

The social/community level of the environment is characterized by the many social networks that support the adolescents' daily life and the work organization. The social and community systems have the potential to either support or impede the adolescent workers' ability to be safe and healthy at work.

Learning about fieldwork. The family unit is an important social context for the Latino adolescent; it has a tremendous impact on the work life of an adolescent farmworker. Most participants reported that their family and friends currently worked in the fields. Much of what the adolescent farmworker knows about work and its associated hazards, he or she has learned through observing and listening to his or her parents and other family members. "My father taught me . . . in the fields. We used to sow onions, potatoes, lettuces, all types of vegetables . . . he taught me to plant all types of plants . . . to harvest." Although these youths may not feel that they can ask their bosses questions about work, they can ask family and friends.

Knowledge about hazards. Although parents, family, and friends are the primary source of information about pesticide hazards, participants also described various social and community sources of information, such as school, training videos, the Internet, and several media sources. They learned about pesticide exposures from observation of others as well as by being told about them. The adolescents described family members or coworkers who had become sick. One participant stated his mother "got a big rash on her hand" when she sprayed some plants. Another reported that a coworker "passed out" and had to be taken away by an ambulance after exposure in a recently sprayed field. In every focus session, adolescents described how their family members, usually their mother and/or father, told them about the

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

hazards of fieldwork. Some participants also described school-based clubs and classes at school, such as their health class, that "talk about hazards."

Managing work and school. Working in the fields may interfere with school attendance and performance. Some participants complained of being too tired following a long day at work to attend summer night school. Others were too tired to do homework: "I'm tired when I get home, and I can't study because I'm very tired." Another stated, "The truth is, we'd like to study if there's the opportunity, but . . . we have to work." On the positive side, some suggested that learning about hazards through video presentation or group sessions might benefit their ability to participate in school discussions: "It will help us with school because we . . . will already know when they begin to talk about this. We could be the ones out of our class to raise our hands all the time and speaking, you know."

Macroenvironment

The macroenvironment, though less tangible than the other levels of influence, is nevertheless likely to have profound effects on the adolescents' work life and their protection (or lack thereof) from hazards. Macroenvironments are reflected in society's attitudes and actions toward these workers. The effects can be direct and indirect.

Barriers to choice. Some comments clearly suggested that these adolescents feel stereotyped because of their ethnicity. This was particularly notable among the non-English-speaking group. "You feel like only Mexicans do this [work in the fields] 'cause that is all you usually see, Mexican people around." The ability to choose the type of work one performs is partially related to societal attitudes. "You really don't have much of an option," stated one respondent. Members of their family "are immigrants . . . and [they] don't have papers or whatever; and the only place they can go that would accept them is in the fields." Another stated that because "papers are fake . . . some are afraid." Some participants stated they had to work because they were poor: "The poverty that we have, that is the thing that makes us work."

Other barriers to choice are language and level of literacy. "I don't know English. . . . I think that is the reason some farmers don't really take precautions, because they know [we] are immigrants, and they can get immigrants in a lot of trouble." And another: "When you are working in the field, you feel like you have no rights." A lack of choice results in workers' taking

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

risks. A sense of powerlessness prevents them from being able to speak out when they perceive that conditions are unsafe because the boss "would probably get mad and fire you right there."

Traditional values. According to several respondents, work is highly valued in the Mexican community, and working at a young age is desirable. "It is the custom for the parents to get their children at a young age and take them to work . . . especially Hispanics." Because of the prevailing work ethic in this population, concern about workplace hazards may be less important. During a conversation about the training that was provided, one youth stated, "Over there in Mexico, they don't teach you how to take care of yourself."

Rules and regulations. Several youths commented on the importance of having regulations aimed at protecting workers. Hazards should be identified, they stated, and there should be "caution" and "hazard" signs to warn workers of known hazards; protective gear should be provided, and the use of protective equipment needs to be enforced. Training should be mandatory, according to one youth: "They need to develop programs to teach us about the hazards." Regulations should be enforced for all: "It's not right that some have protection and others don't while doing a hazardous job." On the other hand, a disregard for regulations provides these youths with the opportunity to work. To get other types of jobs, one has to comply with the age requirement, stated one: "In the fields, there is no lower age limit."

DISCUSSION

Although the findings related to the microenvironment indicated that these adolescent farmworkers are aware that there are risks associated with pesticide exposure, there were varying opinions regarding their perceptions of personal vulnerability. There were two lines of thinking. The first suggested that sickness was an inevitable by-product of their work; the second suggested that the "weak" are the most likely to be vulnerable. Both positions may lead to complacency. In the first case, the worker may be saying, "What's the point, I am going to get sick anyhow. Why bother protecting myself?" In the second case, if they see themselves as fit and "strong," they may not see the need for appropriate precautions. These findings confirm reports by Hunt, Tinoco-Ojanguren, Schwartz, & Halperin (1999) whose ethnographic surveys with adult farmworkers in southern Mexico revealed that they considered pesticide illness as part of the job and something that a

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

healthy person could endure. Other studies have suggested that Mexicans and Mexican Americans often consider the sick and infirm to be vulnerable to pesticide exposure (Lantz, Dupuis, Reding, Krauska, & Lappe, 1994).

Of particular note is the fact that the majority of the barriers to safe work practices seemed to be at the organizational level. Most notable were the struggles with the boss, who was often perceived as demanding and uncaring. Participants also noted environmental conditions that interfered with their ability to carry out safe work practices. Although in several instances, appropriate provisions (i.e., soap, water, washing facilities) were available, there were several reports of inadequate stocking of and inability to access items. Even if supplies were available, the psychological demands of the workplace often precluded these young workers from feeling free to use them. The participants of the present study exhibited a strong sense of responsibility toward their families; these were not a group of self-serving teenagers. Although they expressed a desire to do well in school and to be successful, they accepted their responsibility to their families as a first priority. The majority gave at least a part of their income to their parents or relatives in Mexico. This neglect of self for the good of the greater community may also influence the strength of their resolve (or lack of resolve) to protect their own health.

The descriptions that the adolescents gave regarding the nature of safety training that they have received are particularly disturbing. Castillo, Davis, & Wegman (1999) reported that given the limited experience that youths bring to the workplace, they may require additional time and different approaches to training than adults. Ethnic diversity, language barriers, and low educational attainment of the farmworker population add additional challenges to the task of increasing the occupational health and safety of this working population. Several youths indicated their primary source of information about health hazards and safe work practices were family members, primarily their parents. Recent data indicate that approximately one half of hired farmworkers who are between 14 and 17 years old live on their own, away from their parents (Mines, Gabbard, & Stierman, 1997; U.S. GAO, 1998b). In a 1997 study of adolescent farmworkers in one county in Oregon, McCauley et al. (2002) reported two thirds of the adolescent farmworkers in that study were not accompanied by their parents. Health and safety professionals cannot assume that parents of these adolescent farmworkers will provide agricultural safety education, nor can parents or family members be expected to accurately relay all of the Worker Protection Standard points to teenagers new to the industry.

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

The comments of several participants suggested that these youths are adapting an identity that defines their roles in society. This is particularly evident at the macroenvironment level. They seemed to say, We are Mexicans; Mexicans are destined to work in the fields, thus my life's work is in the fields. Many feel they have few or limited choices. This sense of powerlessness, coupled with traditional family and cultural values and documentation issues, may serve as major deterrents to self-advocacy in terms of health and safety. Programs targeting health and safety must also serve to empower these workers to stay safe and healthy, to feel that they can speak out on their own behalf, and that they can demand to have training materials that they understand and utilize.

It was interesting that some youths indicated that there should be regulations to protect workers, such as notification signs of dangerous areas, training requirements, and owner-supplied protective equipment, yet these regulations are well articulated in the EPA Worker Protection Standard. These findings along with those of others (Arcury, Quandt, Cravey, Elmore, & Russell, 2001; Larson, 2000; McCauley et al., 2002) suggest that the EPA Worker Protection Standard is not functioning as intended. Larson (2000), in an evaluation report of the Worker Protection Standard, reports that training occurs less frequently among the seasonal and migrant farm laborers than it does among other farmworkers. The health of these youths is further compromised by the fact that many began working in agriculture at such young ages and that this may be in conflict with the child labor requirements under the Fair Labor Standards Act (U.S. Department of Labor, 1984). The act indicates that the minimum age for unrestricted nonhazardous agricultural work is 16. For youths younger than 16, work is restricted to after-school hours. Youths under 14 must have parental permission or work alongside their parents. Minors of any age may work on their own family farm. Compared to other industries, agriculture work maintains an entirely different set of child labor regulations, which may not be strictly enforced. If adolescents perceive a lack of regard for basic labor laws, they may also apply nonregard to other work-related regulations, such as certification for pesticide application or use of personal protective equipment.

Limitations and Strengths of the Study

The frank and candid responses of these adolescent farmworkers provided a valuable glimpse into the world of these at-risk workers. A major strength of the present study was that data were obtained directly from the

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

population of interest, and the participants had an opportunity to describe their beliefs, perceptions, and attitudes in their own words. The ability to build on the comments of others served to provide an in-depth understanding of the concerns, as well as the unique strengths that characterize this population. It must be noted, however, that these focus group discussions relied heavily on the skills of the moderator, and in some cases questions were limited due to a defined timeframe. There is also a possibility that moderators or facilitators may have occasionally influenced responses. Although we attempted to obtain variation in the background of the participants by conducting the focus groups in three different agricultural areas, the results cannot be generalized beyond the study participants. The migrant farmworker population is often challenging for researchers to access. Given limited opportunities to obtain more information (as in the present study), researchers may hold findings more sacred than is warranted. Although these limitations were recognized, thoughtful planning of the interview questions and training of the moderator were designed to offset them.

Conclusion

The adolescent migrant farmworker population represents an extremely vulnerable working population. Within the United States, an increasing number of youths working in agriculture are not children working on the family ranch or for small local farms but rather children who work as hired labor on a migrant or seasonal basis or have parents who work as migrant and seasonal workers (U.S. GAO, 1998a). Occupational health and safety professionals maintain that hazards in the work environments must be clearly explained to all workers (Castillo et al., 1999). As was noted in the present study, rote and routine training are not sufficient to protect the health and safety of special populations, such as the migrant adolescent farmworker.

The present study provided an in-depth overview of the perspectives and beliefs of a population that is at high risk for occupational and environmental exposure. Youths in the present study work in a dangerous job that is wrought with short- and long-term risks. During the course of these focus sessions, the need for health education efforts to consider more than personal behaviors and individual change strategies became increasingly clear. A consideration of the multiple influences on health and safety is critically important. The many organizational, social, and cultural barriers that prevent these youths from working safely must be factored into training programs. There is a compelling need to develop and test strategies that will truly be successful in preserving and protecting this vulnerable population.

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

In addition, further studies are needed to fully understand the unique occupational health and safety needs of these workers.

APPENDIX
Examples of Responses by Ecological Level

Microenvironment

> **Protective Behaviors:** Even though I know it's not good for me, I will probably eat right out of the fields, like strawberries, you know, or the berries. I would think, I am hungry. I would just go ahead and eat it, even though I know I should have washed it. A lot of people do that, even if they don't admit it. I see a lot of people doing it. I know it is wrong but I still do it, not a lot, but I do it, just because it is there and it is tempting.

Organization Environment

> **Health and safety training**: I know a lot of farm people give out brochures (that) are in Spanish and English, but come on, some people don't even know how to read. I think there should be groups, like a day before . . . where the owner of the field talks to the workers like a presentation . . . So they talk to them about some things, some kind of training or whatever. So that they are aware of what is going on and what they can do to protect themselves. What they should do if they have a rash or something. A lot of workers are afraid to go up to the owners and say, "I have a rash and do you know what this is from?" They are afraid that they will not be able to come back to work. I think the farmer should take . . . more responsibility than just making sure the work is done. I think they should take the responsibility of the health of the workers.

Social and Community Environment

> **Managing work and school:** (Discussing challenges of starting work at a young age) Because like I was working, (then) my father and mother put me to study, I almost didn't ever study, because I was working in the field since I was very young, and I kept working and . . . I was never in school. . . . We have to study so we can get ahead, because just working . . . the work is always going to be there.
>
> Mexican children start working very young out of need.
>
> I work and study, work and study. . . . I'm tired when I get home, and I can't come (to school) because I'm very tired.

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

Macroenvironment

> **Barriers to choice:** The poverty that we have, that each person has, that is the one thing that makes us work. There are other people that are immigrants, and those don't have papers or whatever. And the only place that they can go that would probably accept them is in the fields. They really don't have much of an option.
>
> Some are afraid . . . we don't have papers, they are fake and . . . I don't speak English either. So they are scared sometimes. I think that is some of the reasons that farmers don't really take precautions because they know we are immigrants, and they can get immigrants in a lot of trouble.

NOTE

1. The authors extend their greatest appreciation to the migrant farmworker community and the Migrant Education Program for their collaboration on this study. This work was funded by the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (R01 OH04230).

REFERENCES

Acosta, M. S., & Lee, B. (2001). *Migrant and seasonal hired adolescent farmworkers: A plan to improve working conditions*. Marshfield, WI: Marshfield Clinic.

Anderson, R. M., Goddard, C. E., Garcia, R., Guzman, J. R., & Vazquez, F. (1998). Using focus groups to identify diabetes care and education issues for Latinos with diabetes. *Diabetes Education, 24*, 618-625.

Arcury, T. A., Quandt, S. A., Cravey, A. J., Elmore, R. C., & Russell, G. B. (2001). Farmworker reports of pesticide safety and sanitation in the work environment. *American Journal of Industrial Medicine, 39*, 487-498.

Arcury, T., Quandt, S. A., & Russell, G. B. (2002). Pesticide safety among farmworkers: Perceived risk and perceived control as factors reflecting environmental justice. *Environmental Health Perspective, 110*(2), 233-240.

Bauer, H. M., Rodriguez, M. A., Quiroga, S. S., & Flores-Oritz, Y. G. (2000). Barriers to health care for abused Latina and Asian immigrant women. *Journal of Health Care for the Poor & Underserved, 11*, 33-44.

Benoliel, J. (1984). Advancing nursing science: Qualitative approaches. *Western Journal of Nursing Research, 7*, 1-8.

Bronfenbrenner, U. (1977). Toward an experimental ecology in human development. *American Psychology, 32*, 513-531.

Castillo, D. N., Davis, L., & Wegman, D. H. (1999). Young workers. *Occupational Medicine, 14*, 519-536.

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

Committee on the Health and Safety Implications of Child Labor. (1998). *Protecting youth at work. Health, safety and development of working children and adolescents in the United States*. Washington, DC: National Academy Press.

Davis, S. (1997). *Child labor in agriculture*. ERIC Clearinghouse on Rural Education and Small Schools (ED405159). Retrieved May 22, 2003, from www.ericfacility.net/databases/ERIC_Digests/ed405159.html

Environmental Protection Agency. (1990). *EPA Worker Protection Act*. Retrieved May 22, 2003, from www.epa.gov/pesticides/safety/workers/workers.htm

Environmental Protection Agency. (1999). *Basic principles of the worker protection standard*. Retrieved May 22, 2003, from www.epa.gov/pesticides/safety/workers/principl.htm

Fleming, L. E., & Herzstein, J. A. (1997). Emerging issues in pesticide health studies. *Occupational Medicine: State of the Art Reviews, 12*(2), 387-397.

Groff, J. Y., Mullen, P. D., Byrd, T., Shelton, A. J., Less, E., & Goode, J. (2000). Decision making, beliefs and attitudes toward hysterectomy: A focus group study with medically underserved women in Texas. *Journal of Women's Health and Gender-Based Medicine, 9*, S39-S50.

Hunt, L. M., Tinoco-Ojanaguren, R., Schwartz, N., & Halperin, D. (1999). Balancing risks and resources: Applying pesticides without using protective equipment in Southern Mexico. In R. A. Hahn & K. W. Harris (Eds.), *Anthropology in public health: Bridging differences in culture and society* (pp. 235-254). New York: Oxford University Press.

Krueger, R. A. (1994). *Focus groups: A practical guide for applied research*. Thousand Oaks, CA: Sage.

Lalonde, B., Rabinowitz, P., Sherfsky, M. L., & Washienko, K. (1997). La Esperanza del Valle: Alcohol prevention novelas for Hispanic youth and their families. *Health Education & Behavior, 24*, 587-602.

Lantz, P. M., Dupuis, L., Reding, D., Krauska, M., & Lappe, K. (1994). Peer discussions of cancer among Hispanic migrant farm workers. *Public Health Reports, 109*, 512-520.

Larson, A. C. (2000). *An assessment of worker training under the Worker Protection Standard* [Executive Summary]. (Prepared for the EPA Office of Pesticide Programs Certification and Worker Protection Branch [EPA Assistance Agreement #CR825080-01-0], Vashon Island, WA).

Linnan, L. A., Sorenson, G., Colditz, G., Klar, D. N., & Emmons, K. M. (2001). Using theory to understand the multiple determinants of low participation in worksite health promotion programs. *Health Education and Behavior, 28*(5), 591-607.

Ludwig-Beymer, P., Blankemeier, J. R., Casas-Byots, C., & Suarez-Balcazar, Y. (1996). Community assessment in a suburban Hispanic community: A description of method. *Journal of Transcultural Nursing, 8*(1), 19-27.

Marshall, C., & Rossman, G. B. (1989). *Designing qualitative research*. Newbury Park, CA: Sage.

Maynard-Tucker, G. (2000). Conducting focus groups in developing countries: Skill training for local bilingual facilitators. *Qualitative Health Research, 10*(3), 396-410.

McCauley, L. A., Sticker, D., Bryan, C., Lasarev, M. R., & Scherer, J. A. (2002). Pesticide knowledge and risk perception among adolescent Latino farmworkers. *Journal of Agricultural Safety and Health, 8*(4), 397-409.

Mines, R., Gabbard, S., & Stierman, A. (1997). *A profile of U.S. farmworkers: Demographics, household composition, income and use of services*. (Prepared for The Commission on Immigration Reform. U.S. Department of Labor Office of the Assistant Secretary for Policy, Washington, DC).

Morgan, D. L. (1998). *Planning focus groups*. Thousand Oaks, CA: Sage.

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

Napolitano, M., & Beltran, M. (1998, November). *The dynamic process of focus groups with agricultural farmworkers: The Oregon experience.* Paper presented at the American Public Health Association Annual Meeting. Washington, DC.

Napolitano, M., Lasarev, M., Beltran, M., Phillips, J., Bryan, C., & McCauley, L. (2002). Un lugar seguro para sus ninos: Development and evaluation of a pesticide education video. *Journal of Immigrant Health, 4*(1), 35-45.

National Safety Council. (2002). The plain facts . . . about the agricultural industry. *Agricultural Safety Fact Sheet.* Retrieved April 17, 2003, from www.nsc.org/issues/agri/indus.htm

Newes-Adeyi, G., Helitzer, D. L., Caulfield, L. E., & Bronner, Y. (2000). Theory and practice: Applying the ecological model to formative research for a WIC training program in New York State. *Health Education and Research, 15*(3), 283-291.

Owen, S. (2001). The practical, methodological, and ethical dilemmas of conducting focus groups with vulnerable clients. *Journal of Advanced Nursing, 36*, 652-658.

Perilla, J. L., Wilson, A. H., Wold, J. L., & Spencer, L. (1998). Listening to migrant voices: Focus group on health issues in south Georgia. *Journal of Community Health Nursing, 15*, 251-263.

Quandt, S. A., Arcury, T. A., Austin, C. K., & Cabrera, L. F. (2001). Preventing occupational exposure to pesticides: Using participatory research with Latino farmworkers to develop an intervention. *Journal of Immigrant Health, 3*, 85-96.

Richard, L., Potvin, L., Kishchuk, N., Prlic, H., & Green, L. W. (1996). Assessment of the integration of the ecological approach in health promotion programs. *American Journal of Health Promotion, 10*, 318-328.

Shu, X. O., Gao, Y. T., Brinton, L. A., Linet, M. S., Tu, J. T., Zheng, W., et al. (1988). A population-based case-control study of childhood leukemia in Shanghai. *Cancer, 62*, 635-644.

U.S. Department of Labor. (1984). *Child labor requirements in agriculture under the Fair Labor Standards Act (Child Labor Bulletin No. 102).* Washington, DC: Author.

U.S. General Accounting Office. (1998a). *Child labor in agriculture: Changes needed to better protect health and educational opportunities* (GAO/HEHS-98-193). Washington, DC: Author.

U.S. General Accounting Office. (1998b). *Child labor in agriculture: Characteristics and legality of work* (GAO/HEHS-98-112R). Washington, DC: Author.

U.S. General Accounting Office. (2000). *Pesticides: Improvements needed to ensure the safety of farmworkers and their children* (GAO/RCED-00-40). Washington, DC: Author.

Williams, G. A., Abbott, R. R., & Taylor, D. K. (1997). Using focus group methodology to develop breast cancer screening programs that recruit African American women. *Journal of Community Health, 22*, 45-56.

Wilson, A. H., Pittman, K., & Wold, J. L. (2000). Listening to the quiet voices of Hispanic migrant children about health. *Journal of Pediatric Nursing, 15*, 137-147.

Downloaded from wjn.sagepub.com at PENNSYLVANIA STATE UNIV on May 8, 2016

Non-cancer health effects of pesticides

Systematic review and implications for family doctors

M. Sanborn MD CCFP FCFP K.J. Kerr MD DIP ENVHEALTH L.H. Sanin MD MPH ScD
D.C. Cole MD MSc FRCPC K.L. Bassil MSc C. Vakil MD CCFP FCFP

ABSTRACT

OBJECTIVE To investigate whether there are associations between exposure to pesticides and 4 chronic non-cancer health effects: dermatologic, neurologic, reproductive, and genotoxic effects.

DATA SOURCES We searched PreMedline, MEDLINE, and LILACS using the key word *pesticide* combined with the term for the specific health effect being searched. Reviewers scanned the references of all articles for additional relevant studies.

STUDY SELECTION Studies since 1992 were assessed using structured inclusion and quality-of-methods criteria. Studies scoring <4 on a 7-point global methodologic quality scale were excluded. In total, 124 studies were included. These studies had a mean quality score of 4.88 out of 7.

SYNTHESIS Strong evidence of association with pesticide exposure was found for all neurologic outcomes, genotoxicity, and 4 of 6 reproductive effects: birth defects, fetal death, altered growth, and other outcomes. Exposure to pesticides generally doubled the level of genetic damage as measured by chromosome aberrations in lymphocytes. Only a few high-quality studies focused on the dermatologic effects of pesticides. In some of these studies, rates of dermatitis were higher among those who had had high exposure to pesticides on the job.

CONCLUSION Evidence from research on humans consistently points to positive associations between pesticide exposure and 3 of the 4 non-cancer health outcomes studied. Physicians have a dual role in educating individual patients about the risks of exposure and in reducing exposure in the community by advocating for restrictions on use of pesticides.

EDITOR'S KEY POINTS

- Due to the unethical nature of cause-effect studies on pesticide exposure, the growing body of literature on pesticide health effects cannot be used to establish a cause-effect relationship between the use of pesticides and non-cancer health effects.
- However, there is consistent evidence in the literature that pesticide exposure does increase the risk of 3 non-cancer health effects (neurologic, reproductive, and genotoxic).

This article has been peer reviewed.
Can Fam Physician 2007;53:1712-1720

ED_001854_00010739-00001

Pesticides: effets sur la santé, outre le cancer

Revue systématique et implications pour le médecin de famille

M. Sanborn MD CCFP FCFP K.J. Kerr MD DIPENVHEALTH L.H. Sanin MD MPH ScD
D.C. Cole MD MSc FRCPC K.L. Bassil MSc C. Vakil MD CCFP FCFP

RÉSUMÉ

OBJECTIF Déterminer s'il existe une association entre l'exposition à des pesticides et 4 types d'effets nocifs chroniques sur la santé, outre le cancer: effets d'ordre dermatologique, neurologique, reproducteur et génotoxique.

SOURCES DES DONNÉES On a consulté PreMedline, MEDLINE et LILACS à l'aide du mot-clé *pesticide* combiné à chacun des termes désignant les effets spécifiques à l'étude. Les analystes ont scruté la bibliographie de chaque article pour identifier toute autre étude pertinente.

CHOIX DES ÉTUDES Le choix des études publiées depuis 1992 était basé sur des critères d'inclusion structurés et des critères de qualité méthodologique. Les études obtenant un score inférieur à 4 sur une échelle de qualité méthodologique globale de 7 points ont été exclues. Au total, 124 études ont été retenues, avec un score de qualité moyen de 4,88 sur 7.

SYNTHÈSE On a trouvé des preuves convaincantes d'une association entre l'exposition aux pesticides et l'ensemble des issues neurologiques, la génotoxicité et 4 des 6 effets sur la reproduction: malformations congénitales, mort fœtale, anomalie de croissance et autres issues. De façon générale, l'exposition aux pesticides a doublé le niveau de dommage génétique tel que mesuré par les modifications chromosomiques dans les lymphocytes. Seules quelques études de bonne qualité ont porté sur les effets dermatologiques des pesticides. Dans certaines de ces études, on a observé un taux plus élevé de dermatites chez ceux qui avaient été fortement exposés en milieu de travail.

CONCLUSION La plupart des données tirées de la recherche chez l'humain indiquent que l'exposition à des pesticides est associée à 3 des 4 problèmes de santé étudiés. Le médecin a le double rôle de renseigner chaque patient sur les risques d'une telle exposition et de promouvoir un usage restreint des pesticides afin de réduire l'exposition dans la communauté.

POINTS DE REPÈRE DU RÉDACTEUR

- En raison de la nature non éthique des études de type cause-effets sur l'exposition aux pesticides, on ne peut utiliser les données de plus en plus nombreuses de la littérature dans ce domaine pour établir une relation de cause à effet entre l'utilisation des pesticides et les effets sur la santé autres que les cancers.
- Il existe toutefois dans la littérature des preuves abondantes confirmant que l'exposition aux pesticides augmente le risque de développer trois effets nocifs autres que cancéreux: effets sur le système nerveux, sur la reproduction et génotoxicité.

Cet article a fait l'objet d'une révision par des pairs.
Can Fam Physician 2007;53:1712-1720

ED_001854_00010739-00002

Pesticides include all classes of chemicals used to kill or repel insects, fungi, vegetation, and rodents.[1,2] It is well accepted that acute poisonings cause health effects, such as seizures, rashes, and gastrointestinal illness.[1-4] Chronic effects, such as cancer and adverse reproductive outcomes, have also been studied extensively, and the results have been interpreted in various ways as evidence that pesticides are safe or are a cause for concern because they can be detrimental to human health. Bylaw debates across Canada have focused public attention on the cosmetic (non-commercial crop) uses of pesticides and the attendant potential risks of chronic low-level exposure.

Family physicians need evidence-based information on the health effects of pesticides to guide their advice to patients and their involvement in community decisions to restrict use of pesticides. A systematic review by the Ontario College of Family Physicians' Environmental Health Committee was done as a basis for informing family physicians' approach to disseminating information on pesticides to patients and communities.[5]

This article reports on a systematic review of articles published between 1992 and 2003 on 4 non-cancer chronic health effects thought to be associated with exposure to pesticides: dermatologic, neurologic, reproductive, and genotoxic effects. Cardiovascular, respiratory, and learning disability outcomes were not included in the review because of resource constraints. Findings on pesticides and cancer outcomes are reported in another article.[6]

DATA SOURCES

Primary peer-reviewed studies were located using PreMedline, MEDLINE, and LILACS (Spanish- and Portuguese-language articles) databases. All searches included the key MeSH heading "pesticides" combined with the MeSH heading for the health effects under study. Reviewers systematically scanned the references of all articles for additional relevant studies.

Dr Sanborn *is an Assistant Clinical Professor in the Department of Family Medicine at McMaster University in Hamilton, Ont.* **Dr Kerr** *is a lecturer in the Department of Family and Community Medicine at the University of Toronto in Ontario.* **Dr Sanin** *is a Professor in the Department of Public Health Sciences at the Universidad Autonoma de Chihuahua in Mexico.* **Dr Cole** *is an Associate Professor of Medicine and* **Ms Bassil** *is a doctoral candidate in the Department of Public Health Sciences at the University of Toronto.* **Dr Vakil** *is an Assistant Professor in the Department of Family Medicine at Queen's University in Kingston, Ont.*

Study selection

The 3 criteria for inclusion in the assessment were being peer reviewed, being a study of human health effects related to pesticide exposure, and being published between 1992 and 2003. A systematic review done in 1993 had covered pesticide health effect studies up to 1991.[7] A total of 150 studies were retrieved by the search for the 4 categories of health effects (**Table 1**). Two independent reviewers each filled out 5-page Data Extraction Forms for each study. A 7-point Likert-type Global Methodological Quality Assessment Scale was used to assess all papers; 26 papers scored <4 out of 7 and were excluded.

SYNTHESIS

Dermatologic effects

Skin is the primary route of exposure to pesticides for sprayers, handlers, and people using repellants. Excluding acute poisonings, contact dermatitis is thought to be the most common health effect of pesticides, through either irritant or allergic mechanisms.[8] Along with eye injuries, it is the health effect most likely to be seen in the office[2] and might be the only indicator of exposure.

In the 10 studies reviewed[9-18] (none from Canada), it was difficult to assess the prevalence of skin disorders attributable to pesticides. In agricultural workers with contact dermatitis, sensitization to both plant material and pesticides was documented,[9,16] but most study designs did not allow attribution of rashes specifically to pesticide exposure. One study that used a biomarker for pesticide exposure found a dose-response relationship between dermatitis and years of fungicide exposure or poor application practices[13]; 61% of pesticide-exposed agricultural workers and 31% of controls had dermatitis ($P<.001$).[13] Pet groomers who gave more than 75 pyrethrin flea treatments per year had more rashes (odds ratio [OR] 2.04, 95% confidence interval [CI] 1.02 to 4.09) and more eye symptoms (OR 4.75, 95% CI 1.14 to 18.23) than those who gave fewer treatments.[10]

Neurotoxicity

Long-term effects of pesticides on the nervous system include cognitive and psychomotor dysfunction, and neurodegenerative and neurodevelopmental effects. Pesticide poisonings result in well-described acute and chronic neurotoxic syndromes.[19] Chronic effects from low or moderate exposures have been less well documented.

Our systematic review began with 4 relevant studies, including a metanalysis on Parkinson disease (PD) and pesticide exposure[20]; 41 primary studies[21-62] were of adequate quality. Most studies analyzed covariates that might affect nervous system function. Differentiating between the effects of chronic or cumulative exposure and current

ED_001854_00010739-00003

Table 1. Summary of studies reviewed

HEALTH EFFECT	NO. OF STUDIES FOUND	NO. OF STUDIES INCLUDED*	SUMMARY OF RESULTS	MEAN GLOBAL SCORE OF STUDIES INCLUDED*
Dermatologic effects	11	10	7/10 studies positive for dermatitis with pesticide exposure	4.50
Neurotoxicity	60	41	39/41 studies positive for increase in 1 or more neurologic abnormalities with pesticide exposure	4.99
Reproductive outcomes	64	59	Birth defects: 14/15 studies positive; time to pregnancy: 5/8 studies positive; fertility: 7/14 studies positive; altered growth: 7/10 studies positive; fetal death: 9/11 studies positive; other outcomes: 6/6 studies positive	4.83
Genotoxicity	15	14	11/14 studies positive for increased chromosome aberrations with pesticide exposure†	5.03

*Assessors scored each paper on a 7-point scale for methodologic quality from 1—very poor to 7—excellent. Papers scoring <4 were excluded.
†Figure 1 aggregates results from all 14 genotoxicity studies.

intense exposure can be difficult. Unfortunately for many exposed populations (eg, Ecuadorian farm families[29,30]), mixed past poisoning, cumulative exposure, and current work and home exposures are overlaid.

Maternal, in-utero, and early childhood exposures are likely all involved in producing neurodevelopmental effects in preschool children in pervasive exposure situations, such as Mexican valley agriculture.[40] Only 2 studies of effects including children were found,[40,42] despite considerable concern about the effects of pesticide exposure on sensitive populations, such as inner-city children.[4]

Most studies documented mixed pesticide exposures. Cross-sectional studies often included exposure biomarkers, such as herbicide or alkyl phosphates in urine or acetylcholinesterase levels in blood. Some studies were exceptional in documenting specific exposures, for example, fumigants.[28]

General neurotoxic morbidity. General malaise and mild cognitive dysfunction might be the earliest neurotoxic responses to pesticide exposure.[62] Most studies using validated questionnaires and performance tests found an increased prevalence of symptoms or mood changes, as well as alterations in neurobehavioural performance and cognitive function.

Studies of the mental and emotional effects of pesticides found associations for current minor psychiatric morbidity,[27] depression,[55] suicide among Canadian farmers,[49] and death from mental disorders,[60] particularly neurotic disorders in women. Keifer et al[42] found substantially higher rates of mental and emotional symptoms in residents (including adolescents) exposed to spray-plane drift compared with those not exposed.

Associations between previous pesticide poisonings, particularly from organophosphates and carbamates, and decreases in current neurobehavioural function were most consistently positive. Those with greater exposures (eg, termiticide applicators[31] or farmers handling concentrates[50]) also showed more consistent decreases in function. Together, these studies provide important evidence of the subclinical effects of pesticides on the nervous system. These effects might become clinically manifest in a few cases.

Neurodegenerative disease. Most of these studies examined mixed occupational exposures. Some focused on herbicides. Health outcomes varied from PD on clinical examination through adjusted incidence of hospitalization for PD to deaths from PD. All found positive associations between exposure and PD. Combined with the earlier meta-analysis,[20] the results of 15 out of 26 studies were positive for associations between pesticide exposure and PD. These data provide remarkably consistent evidence of a relationship between PD and past exposure to pesticides on the job (OR 1.8 to 2.5).

Evidence of other neurodegenerative effects of pesticides is also accumulating. Of 2 studies on Alzheimer disease, 1[38] found no association and 1[24] found an association in men. A study on amyotrophic lateral sclerosis[46] found consistently elevated adjusted ORs associated with pesticide exposure in both men and women.

Reproductive outcomes

Six distinct groups of reproductive outcomes were chosen for study: birth defects, fecundability, fertility, altered growth, fetal death, and mixed outcomes.

Birth defects. Fifteen studies from 9 countries[63-77] examined associations between pesticides and birth defects. The studies consistently showed increased risk with pesticide exposure. Specific defects included

ED_001854_00010739-00004

limb reductions,[64,67,73] urogenital anomalies,[68,73,75] central nervous system defects,[68,73] orofacial clefts,[74] heart defects,[66,67] and eye anomalies.[77] The rate of any birth defect was also increased by parental exposure to pesticides.[66-71,74,76] In many studies, there were multiple exposures. Two studies identified specific pesticides: glyphosate[64] and the pyridil derivatives.[69]

Time to pregnancy. Eight studies from 6 countries[78-85] analyzed associations between pesticide exposure and time to pregnancy. Data on pesticide exposures and outcome were collected retrospectively by self-report. Five studies showed positive associations, and 3 showed no association between pesticide exposure and time to pregnancy. All 3 papers showing no association collected exposure and outcome information from men only.[79-81]

Fertility. Fertility refers to the ability to become pregnant in 1 year and includes male and female factors, such as semen quality and infertility. Twelve studies from 7 countries were reviewed.[86-99] Results were mixed; several studies found no associations between pesticide exposure and sperm abnormalities. One study found an association between organophosphate metabolites and sperm sex aneuploidies[94]; another study found an association between erectile dysfunction and pesticide exposure.[95] One study found an increased risk of infertility among women who worked with herbicides in the 2 years before attempted conception.[98]

Altered growth. Low birth weight, prematurity, and intrauterine growth restriction are not only important determinants of health during the first year of life, but also of chronic diseases of adulthood.[100] Ten studies, mainly from Europe and North America,[76,77,101-108] examined pesticide effects on fetal growth. Seven of these showed positive associations between agricultural pesticide exposure and altered fetal growth. Two pesticides implicated in the positive studies were pyrethroids and chlorpyrifos, the latter a commonly used ant-killer now being phased out because of health effects.

Fetal death. Fetal death includes spontaneous abortion, fetal death, stillbirth, and neonatal death. Results were consistent across several study designs; 9 of 11 studies[64,76,77,109-116] found positive associations with pesticide exposure. The Ontario Farm Study results suggested critical windows when pesticide exposure is most harmful. Preconception exposure was associated with early first-trimester abortions, and post-conception exposure was associated with late spontaneous abortions.[110] In a study from the Philippines,[76] risk of spontaneous abortion was 6 times higher in farming households with heavy pesticide use than it was among those using integrated pest management (which results in reduced pesticide use).

Other reproductive outcomes. Seven studies examined other reproductive outcomes, such as sex ratio, placental quality, and developmental delay after in-utero exposure.[64,107,117-121] A Mexican study[115] found higher rates of placental infarction in rural women exposed to organophosphate insecticides; exposure was biomarker-documented with depressed red blood cell cholinesterase levels. Results on altered sex ratios were inconsistent.[64,114]

Genotoxicity

Genotoxicity is the ability of a pesticide to cause intracellular genetic damage. In all reported studies, it was measured as percent chromosome aberrations per 100 peripheral blood lymphocytes. Increased frequency of chromosome aberrations was a predictor of increased cancer rates in a large prospective cohort study (n=5271) with follow-up for 13 to 23 years.[122] Similar studies of associations with reproductive outcomes have not been done.

Important confounders are exposures that cause genetic damage: smoking, alcohol consumption, diet, caffeine intake, radiation, and mutagenic drugs. The latter are important since drugs such as methotrexate are now used widely for rheumatoid arthritis and Crohn disease. Few studies measured all confounders; most excluded smokers and subjects who had x-rays or took mutagenic drugs during the previous year.

Positive associations between pesticide exposure and elevated percent chromosome aberrations were found in 11 of 14 studies.[123-136] Two studies showing no association had taken blood samples during low-exposure seasons.[128,129] Two studies pointed to synthetic pyrethrins[134] and organophosphates[135] as highly genotoxic. Aggregate results from all 14 studies are shown in **Figure 1**; pesticide exposure doubled the frequency of chromosome aberrations. In clinical practice, these aberrations could present as spontaneous abortion, birth defects, sperm abnormalities, or cancer risk.

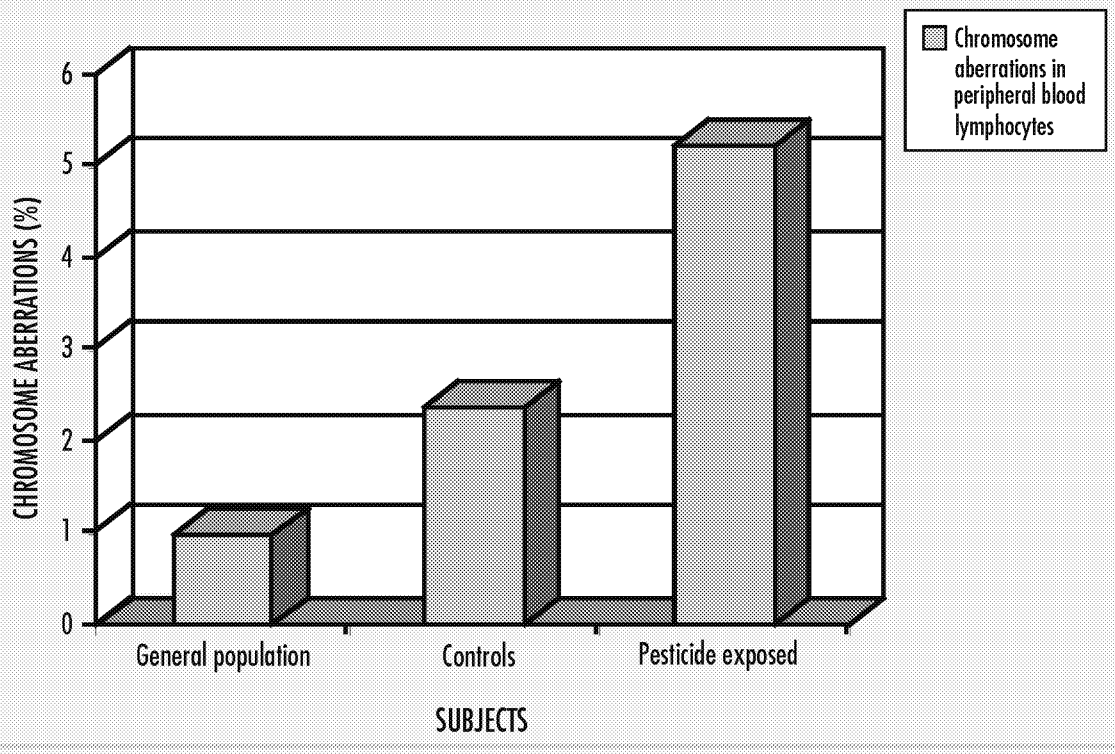
DISCUSSION

For the 4 non-cancer effects reviewed, the strongest evidence of association with pesticide exposure was found for neurologic abnomalities, 4 out of 6 reproductive outcomes, and genotoxicity effects (**Table 1**).

The most striking feature of the results of this systematic review is the consistency of evidence showing that pesticide exposure increases the risk of 3 non-cancer health effects: neurologic, reproductive, and genotoxic effects. The results are consistent with those of other reviews published before[20] and since[137,138] this review was completed. Results of dermatologic studies are less consistent and of poorer quality and indicate the need for a primary care prevalence study of pesticide-related skin conditions.

ED_001854_00010739-00005

Figure 1. Percent of chromosome aberrations for 500 control and 529 pesticide exposed subjects in 14 genotoxicity studies compared with the general population



Assessment of exposure remains a key problem that is being addressed in newer studies by enhanced biomonitoring. For example, a cohort of children now being followed longitudinally had cord-blood levels of several pesticides measured at birth[139] and by maternal air and blood sampling during pregnancy.[140] The role of genetics in the ability to metabolize pesticides, which varies widely among ethnic groups,[141] is being incorporated into more study designs[41,124,142] and should refine our knowledge and explain some inconsistencies in the international literature.

Limitations

The major limitation of studies of the health effects of pesticides is their inability to demonstrate cause-effect relationships. Study subjects cannot be deliberately exposed to potentially harmful toxins, and few exposure-reduction options are tested in randomized controlled trials. The evidence generated by well-constructed clinical and epidemiologic observational studies is the highest level of evidence we can ethically obtain.

The studies reviewed have methodologic problems, such as exposure misclassification and inadequate exposure assessment (causing mixed results) and recall bias (in retrospective case-control studies). Unpublished literature on health effects that was not accessed would be useful to determine whether there is a publication bias toward positive studies. The effect of unpublished positive or negative studies generated by chemical industry–funded research also cannot be assessed. Many good-quality studies were found in the review, however, and taken together, the results provide sufficient cause for family doctors to educate patients and to act to prevent unnecessary pesticide exposure.

Conclusion

This systematic review provides clear evidence that pesticide exposure increases risk to human health across a range of exposure situations and vulnerable populations. Public support for restrictions on pesticide use is growing; 71% of respondents supported provincewide restrictions in a recent Ontario poll.[143] The Canadian Association of Physicians for the Environment[144] and national pediatric and public health groups in Canada and the United States[145-8] have expressed concern about health effects from cosmetic use of pesticides and recommended that physicians participate in reduction efforts.

Family doctors have a dual role in reducing pesticide exposures. First, during individual encounters, we can educate patients about pesticide health effects,[149] monitor through exposure histories[150] and laboratory tests,[151] and advise when we believe the level of exposure poses a health threat. We should encourage harm reduction through use of protective equipment when pesticide exposure is necessary. Advice about use of protective

ED_001854_00010739-00006

Practice tips based on the review

1. Advise patients to avoid pesticide exposure during critical reproductive periods. This includes occupational, indoor, lawn, and garden exposure to pesticides.
- For women, the critical period for early spontaneous abortion is before pregnancy, and for late spontaneous abortion, the first trimester.
- For men, the critical period is the 3 months of spermatogenesis before conception.

2. Take a pesticide-exposure history from patients who have adverse reproductive events, such as intrauterine growth restriction, prematurity, inability to conceive in 1 year, or birth defects.
- Birth defects are associated with both maternal and paternal exposure to pesticides before conception and during the first trimester.
- Most exposures are work related, but transposition of the great vessels is increased with household exposure.

3. Screen patients with a history of exposure to pesticides for neurologic conditions (which can be subtle).
- Occupationally exposed adults are at increased risk of neurologic symptoms, including neurobehavioural changes and Parkinson disease.

4. Use biomonitoring as an effective tool to reduce exposure. Biomonitoring for recent (within 3 months) organophosphate insecticide exposure is done by ordering red blood cell cholinesterase tests.[2] The test is covered by the Ontario Health Insurance Plan; in other provinces, it costs $25 to $100, but might be covered for exposed workers.

equipment is an important and neglected area of family practice,[152] although it is an effective intervention for reducing pesticide exposure.[133,153] Then, in our role as public and community health advocates, we need to educate the public about the health effects of pesticide use. We need to reinforce community efforts to reduce cosmetic use of pesticides that can disproportionally affect children, pregnant women, and elderly people.

Contributors

Dr Sanborn, Dr Kerr, Dr Sanin, Dr Cole, Ms Bassil, *and* **Dr Vakil** *contributed to concept and design of the study, data analysis and interpretation, and preparing the article for submission.*

Competing interests

The systematic review was completed with funding from the Laidlaw Foundation and the Ontario College of Family Physicians. **Dr Sanborn, Dr Kerr,** *and* **Dr Vakil** *received honoraria from the Ontario College of Family Physicians for working on this article.* **Dr Cole** *has received funding from the International Development Research Centre and the Canadian Institutes for Health Research around pesticides but not for this review. Although* **Ms Bassil** *currently works in the Environmental Protection Office at Toronto Public Health in Ontario, she was not employed there while working on the systematic review.* **Dr Vakil** *has received teaching honoraria from the Ontario College of Family Physicians and the International Joint Commission Health Professional Task Force.*

Correspondence to: **Dr Margaret Sanborn**, *Chesley Medical Clinic, Box 459, Chesley, ON N0G 1L0; e-mail* **msanborn@sbghc.on.ca**

References

1. Guidotti TL, Gosselin P, editors. The Canadian guide to health and the environment. Edmonton, Alta: University of Alberta Press and Duval House Publishing; 1999.
2. Reigert JR, Roberts JR. *Recognition and management of pesticide poisonings.* 5th ed. Washington, DC: United States Environmental Protection Agency; 1999. Available from: **www.epa.gov/pesticides/safety/healthcare/handbook/handbook.pdf**. Accessed 2007 September 12.
3. Alarcon WA, Calvert GM, Blondell JM, Mehler LN, Sievert J, Propeck M, et al. Acute illnesses associated with pesticide exposure at schools. *JAMA* 2005;294(4):455-65.
4. Landrigan PJ, Claudio L, Markowitz SB, Brenner BL, Romero H, Wetmur JG, et al. Pesticides and inner-city children: exposures, risks and prevention. *Environ Health Perspect* 1999;107(Suppl 3):431-7.
5. Sanborn M, Cole D, Kerr K, Vakil C, Sanin LH, Bassil K. Pesticides literature review. Toronto, Ont: Ontario College of Family Physicians; 2004. Available from: **www.ocfp.on.ca/local/files/Communications/Current%20Issues/Pesticides/Final%20Paper%2023APR2004.pdf**. Accessed 2007 August 29.
6. Bassil KL, Vakil C, Sanborn MD, Cole DC, Kaur JS, Kerr KJ. Cancer health effects of pesticides: a systematic review. *Can Fam Physician* 2007;53:1704-11.
7. Maroni M, Fait A. Health effects in man from long-term exposure to pesticides. A review of the 1975-1991 literature. *Toxicology* 1993;78(1-3):1-180.
8. Spiewak R. Pesticides as a cause of occupational skin diseases in farmers. *Ann Agricultur Environ Med* 2000;8:1-5.
9. Bruynzeel DP, de Boer EM, Brouwer EJ, de Wolff FA, de Haan P. Dermatitis in bulb growers. *Contact Dermatitis* 1993;29:11-5.
10. Bukowski J, Brown C, Korn LR, Meyer LW. Prevalence of and potential risk factors for symptoms associated with insecticide use among animal groomers. *J Occup Environ Med* 1996;38:528-34.
11. Castro-Gutierrez N, McConnell R, Andersson K, Pacheco-Anton F, Hogstedt C. Respiratory symptoms, spirometry and chronic occupational paraquat exposure. *Scand J Work Environ Health* 1997;23:421-7.
12. Cellini A, Offidani A. An epidemiological study on cutaneous diseases of agricultural workers authorized to use pesticides. *Dermatology* 1994;189:129-32.
13. Cole DC, Carpio F, Math JJ, Leon N. Dermatitis in Ecuadorian farm workers. *Contact Dermatitis* 1997;37:1-8.
14. Cooper SP, Downs T, Burau K, Buffler PA, Tucker S, Whitehead L, et al. A survey of actinic keratoses among paraquat production workers and a non-exposed friend reference group. *Am J Ind Med* 1994;25:335-47.
15. Guo YL, Wang BJ, Lee CC, Wang JD. Prevalence of dermatoses and skin sensitization associated with use of pesticides in fruit farmers of southern Taiwan. *Occup Environ Med* 1996;53:427-31.
16. Paulsen E. Occupational dermatitis in Danish gardeners and greenhouse workers (II). Etiological factors. *Contact Dermatitis* 1998;38:14-9.
17. Penagos HG. Contact dermatitis caused by pesticides among banana plantation workers in Panama. *Int J Occup Environ Health* 2002;8:14-8.
18. Rademaker M. Occupational contact dermatitis among New Zealand farmers. *Australas J Dermatol* 1998;39:164-7.
19. Savage EP, Keefe TJ, Mounce LM, Heaton RK, Lewis JA, Burcar BJ. Chronic neurological sequelae of acute organophosphate pesticide poisoning. *Arch Environ Health* 1988;43:38-45.
20. Priyadarshi A, Khuder SA, Schaub EA, Shrivastava S. A meta-analysis of Parkinson's disease and exposure to pesticides. *Neurotoxicology* 2000;21(4):435-40.
21. Amado F, Carvallo B, Silva JI, Londono JL, Restrepo H. Prevalencia de discromatopsia adquirida y exposicion a plaguicidas y a radiacion ultravioleta solar. *Rev Fac Nac Salud Publica* 1997;15:(1):69-93.
22. Ames RG, Steenland K, Jenkins B, Chrislip D, Russo J. Chronic neurologic sequelae to cholinesterase inhibition among agricultural pesticide applicators. *Arch Environ Health* 1995;50:440-4.
23. Baldi I, Filleul L, Mohammed-Brahim B, Fabrigoule C, Dartigues JF, Schwall S, et al. Neuropsychologic effects of long-term exposure to pesticides: results from the French Phytoner study. *Environ Health Perspect* 2001;109:839-44.
24. Baldi I, Lebailly P, Mohammed-Brahim B, Letenneur L, Dartigues JF, Brochard P. Neurodegenerative diseases and exposure to pesticides in the elderly. *Am J Epidemiol* 2003;157:409-14.
25. Bazylewicz-Walczak B, Majczakowa W, Szymczak M. Behavioral effects of occupational exposure to organophosphorous pesticides in female greenhouse planting workers. *Neurotoxicology* 1999;20:819-26.
26. Beach JR, Spurgeon A, Stephens R, Heafield T, Calvert IA, Levy LS, et al. Abnormalities on neurological examination among sheep farmers exposed to organophosphorous pesticides. *Occup Environ Med* 1996;53:520-5.

ED_001854_00010739-00007

27. Bowler RM, Mergler D, Huel G, Cone JE. Psychological, psychosocial, and psychophysiological sequelae in a community affected by a railroad chemical disaster. *J Traum Stress* 1994;7:601-24.
28. Calvert GM, Mueller CA, Fajen JM, Chrislip DW, Russo J, Briggle T, et al. Health effects associated with sulfuryl fluoride and methyl bromide exposure among structural fumigation workers. *Am J Public Health* 1998;88:1774-80.
29. Cole DC, Carpio F, Julian J, Leon N. Assessment of peripheral nerve function in an Ecuadorian rural population exposed to pesticides. *J Toxicol Environ Health A* 1998;55:77-91.
30. Cole DC, Carpio F, Julian J, Leon N, Carbotte R, De Almeida H. Neurobehavioral outcomes among farm and nonfarm rural Ecuadorians. *Neurotoxicol Teratol* 1997;19:277-86.
31. Dick RB, Steenland K, Krieg EF, Hines CJ. Evaluation of acute sensory-motor effects and test sensitivity using termiticide workers exposed to chlorpyrifos. *Neurotoxicol Teratol* 2001;23:381-93.
32. Engel LS, Keifer MC, Checkoway H, Robinson LR, Vaughan TL. Neurophysiological function in farm workers exposed to organophosphate pesticides. *Arch Environ Health* 1998;53:7-14.
33. Engel LS, Checkoway H, Keifer MC, Seixas NS, Longstreth WT Jr, Scott KC, et al. Parkinsonism and occupational exposure to pesticides. *Occup Environ Med* 2001;58:582-9.
34. Ernest K, Thomas M, Paulose M, Rupa V, Gnanamuthu C. Delayed effects of exposure to organophosphorus compounds. *Ind J Med Res* 1995;101:81-4.
35. Farahat TM, Abdelrasoul GM, Amr MM, Shebl MM, Farahat FM, Anger WK. Neurobehavioural effects among workers occupationally exposed to organophosphorous pesticides. *Occup Environ Med* 2003;60:279-86.
36. Faria NM, Facchini LA, FassaAG, Tomasi E. [A cross-sectional study about mental health of farm-workers from Serra Gaucha (Brazil)]. *Revista de Saude Publica* 1999;33:391-400.
37. Fiedler N, Kipen H, Kelly-McNeil K, Fenske R. Long-term use of organophosphates and neuropsychological performance. *Am J Ind Med* 1997;32:487-96.
38. Gauthier E, Fortier I, Courchesne F, Pepin P, Mortimer J, Gauvreau D. Environmental pesticide exposure as a risk factor for Alzheimer's disease: a case-control study. *Environ Res* 2001;86:37-45.
39. Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Richardson RJ. The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. *Neurology* 1998;50:1346-50.
40. Guillette EA, Meza MM, Aquilar MG, Soto AD, Garcia IE. An anthropological approach to the evaluation of preschool children exposed to pesticides in Mexico. *Environ Health Perspect* 1998;106(6):347-53.
41. Hubble JP, Kurth JH, Glatt SL, Kurth MC, Schellenberg GD, Hassanein RE, et al. Gene-toxin interaction as a putative risk factor for Parkinson's disease with dementia. *Neuroepidemiology* 1998;17:96-104.
42. Keifer M, Rivas F, Moon JD, Checkoway H. Symptoms and cholinesterase activity among rural residents living near cotton fields in Nicaragua. *Occup Environ Med* 1996;53:726-9.
43. Liou HH, Tsai MC, Chen CJ, Jeng JS, Chang YC, Chen SY, et al. Environmental risk factors and Parkinson's disease: a case-control study in Taiwan. *Neurology* 1997;48:1583-8.
44. London L, Nell V, Thompson ML, Myers JE. Effects of long-term organophosphate exposures on neurological symptoms, vibration sense and tremor among South African farm workers. *Scand J Work Environ Health* 1998;24:18-29.
45. McConnell R, Keifer M, Rosenstock L. Elevated quantitative vibrotactile threshold among workers previously poisoned with methamidophos and other organophosphate pesticides. *Am J Ind Med* 1994;25:325-34.
46. McGuire V, Longstreth WT Jr, Nelson LM, Koepsell TD, Checkoway H, Morgan MS, et al. Occupational exposures and amyotrophic lateral sclerosis. A population-based case-control study. *Am J Epidemiol* 1997;145:1076-88.
47. Misra UK, Prasad M, Pandey CM. A study of cognitive functions and event related potentials following organophosphate exposure. *Electromyogr Clin Neurophysiol* 1994;34:197-203.
48. Petrovitch H, Ross GW, Abbott RD, Sanderson WT, Sharp DS, Tanner CM, et al. Plantation work and risk of Parkinson disease in a population-based longitudinal study. *Arch Neurol* 2002;59:1787-92.
49. Pickett W, King WD, Lees RE, Bienefeld M, Morrison HI, Brison RJ. Suicide mortality and pesticide use among Canadian farmers. *Am J Ind Med* 1998;34:364-72.
50. Pilkington A, Buchanan D, Jamal GA, Gillham R, Hansen S, Kidd M, et al. An epidemiological study of the relations between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy and neuropsychological abnormalities in sheep farmers and dippers. *Occup Environ Med* 2001;58:702-10.
51. Ritz B, Yu F. Parkinson's disease mortality and pesticide exposure in California 1984-1994. *Int J Epidemiol* 2000;29:323-9.
52. Sack D, Linz D, Shukla R, Rice C, Bhattacharya A, Suskind R. Health status of pesticide applicators: postural stability assessments. *J Occup Med* 1993;35:1196-202.
53. Srivastava AK, Gupta BN, Bihari V, Mathur N, Srivastava LP, Pangtey BS, et al. Clinical, biochemical and neurobehavioural studies of workers engaged in the manufacture of quinalphos. *Food Chem Toxicol* 2000;38:65-9.
54. Stallones L, Beseler C. Pesticide illness, farm practices, and neurological symptoms among farm residents in Colorado. *Environ Res* 2002;90:89-97.
55. Stallones L, Beseler C. Pesticide poisoning and depressive symptoms among farm residents. *Ann Epidemiol* 2002;12:389-94.
56. Steenland K, Jenkins B, Ames RG, O'Malley M, Chrislip D, Russo J. Chronic neurological sequelae to organophosphate pesticide poisoning. *Am J Public Health* 1994;84:731-6.
57. Steenland K, Dick RB, Howell RJ, Chrislip DW, Hines CJ, Reid TM, et al. Neurologic function among termiticide applicators exposed to chlorpyrifos. *Environ Health Perspect* 2000;108:293-300.
58. Stephens R, Spurgeon A, Calvert IA, Beach J, Levy LS, Berry H, et al. Neuropsychological effects of long-term exposure to organophosphates in sheep dip. *Lancet* 1995;345:1135-9.
59. Tuchsen F, Jensen AA. Agricultural work and the risk of Parkinson's disease in Denmark, 1981-1993. *Scand J Work Environ Health* 2000;26:359-62.
60. van Wijngaarden E. Mortality of mental disorders in relation to potential pesticide exposure. *J Occup Environ Med* 2003;45(5):564-8.
61. Wesseling C, Keifer M, Ahlbom A, McConnell R, Moon JD, Rosenstock L, et al. Long-term neurobehavioral effects of mild poisonings with organophosphate and n-methyl carbamate pesticides among banana workers. *Int J Occup Environ Health* 2002;8:27-34.
62. Kamel F Hoppin JA. Association of pesticide exposure with neurologic dysfunction and disease. *Environ Health Perspect* 2000;112(9):950-8.
63. Engel LS, O'Meara ES, Schwartz SM. Maternal occupation in agriculture and risk of limb defects in Washington State, 1980-1993. *Scand J Work Environ Health* 2000;26:193-8.
64. Garry VF, Harkins ME, Erickson LL, Long-Simpson LK, Holland SE, Burroughs BL. Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota, USA. *Environ Health Perspect* 2002;110:441-9.
65. Garry VF, Harkins ME, Lyubimov A, Erickson LL, Long L. Reproductive outcomes in the women of the Red River Valley of the North. I. The spouses of pesticide applicators: pregnancy loss, age at menarche, and exposure to pesticides. *J Toxicol Environ Health A* 2002;65:769-86.
66. Loffredo CA, Silbergeld EK, Ferencz C, Zhang J. Association of transposition of the great arteries in infants with maternal exposures to herbicides and rodenticides. *Am J Epidemiol* 2001;153:529-36.
67. Shaw GM, Wasserman CR, O'Malley CD, Nelson V, Jackson RJ. Maternal pesticide exposure from multiple sources and selected congenital anomalies. *Epidemiology* 1999;10:60-6.
68. Garcia-Rodriguez J, Garcia-Martin M, Nogueras-Ocana M, de Dios Luna-del-Castillo J, Espigares-Garcia M, Olea N, et al. Exposure to pesticides and cryptorchidism: geographical evidence of a possible association. *Environ Health Perspect* 1996;104:1090-5.
69. Garcia AM, Benavides FG, Fletcher T, Orts E. Paternal exposure to pesticides and congenital malformations. *Scand J Work Environ Health* 1998;24:473-80.
70. Garcia AM, Fletcher T, Benavides F, Orts E. Parental agricultural work and selected congenital malformations. *Am J Epidemiol* 1999;149:64-74.
71. Rojas A, Ojeda ME, Barraza X. [Congenital malformations and pesticide exposure]. *Revista Medica Chile* 2000;128:399-404.
72. Medina-Carrilo L, Rivas-Solis F, Fernandez-Arguelles R. [Risk for congenital malformations in pregnant women exposed to pesticides in the state of Nayarit, Mexico]. *Ginecol Obstet Mex* 2002;70:538-44.
73. Kristensen P, Irgens LM, Andersen A, Bye AS, Sundheim L. Birth defects among offspring of Norwegian farmers, 1967-1991. *Epidemiology* 1997;8:537-44.
74. Nurminen T, Rantala K, Kurppa K, Holnberg PC. Agricultural work during pregnancy and selected structural malformations in Finland. *Epidemiology* 1995;6:23-30.
75. Weidner IS, Moller H, Jensen TK, Skakkebaek N. Cryptorchidism and hypospadias in sons of gardeners and farmers. *Environ Health Perspect* 1998;106:793-6.
76. Crisostomo L, Molina VV. Pregnancy outcomes among farming households of Nueva Ecija with conventional pesticide use versus integrated pest management. *Int J Occup Environ Health* 2002;8:232-42.
77. Dimich-Ward H, Hertzman C, Teschke K, Hershler R, Marion SA, Ostry A, et al. Reproductive effects of paternal exposure to chlorophenate wood preservatives in the sawmill industry. *Scand J Work Environ Health* 1996;22(4):267-73. Erratum in: *Scand J Work Environ Health* 1998;24(5):416.
78. Abell A, Juul S, Bonde JP. Time to pregnancy among female greenhouse workers. *Scand J Work Environ Health* 2000;26:131-6.
79. Larsen SB, Joffe M, Bonde JP. Time to pregnancy and exposure to pesticides in Danish farmers. ASCLEPIOS Study Group. *Occup Environ Med* 1998;55:278-83.
80. Thonneau P, Larsen SB, Abell A, Clavert A, Bonde JP, Ducot B, et al. Time to pregnancy and paternal exposure to pesticides in preliminary results from Danish and French studies. ASCLEPIOS. *Scand J Work Environ Health* 1999;25(Suppl 1):62-3.
81. Thonneau P, Abell A, Larsen SB, Bonde JP, Joffe M, Clavert A, et al. Effects of pesticide exposure on time to pregnancy: results of a multicenter study in France and Denmark. ASCLEPIOS Study Group. *Am J Epidemiol* 1999;150:157-63.
82. Sallmen M, Liesivuori J, Taskinen H, Lindbohm ML, Anttila A, Aalto L, et al. Time to pregnancy among the wives of Finnish greenhouse workers. *Scand J Work Environ Health* 2003;29:85-93.
83. Petrelli G, Figa-Talamanca I. Reduction in fertility in male greenhouse workers exposed to pesticides. *Eur J Epidemiol* 2001;17:675-7.
84. de Cock J, Westveer K, Heederik D, te Velde E, van Kooij R. Time to pregnancy and occupational exposure to pesticides in fruit growers in The Netherlands. *Occup Environ Med* 1994;51:693-9.
85. Curtis KM, Savitz DA, Weinberg CR, Arbuckle TE. The effect of pesticide exposure on time to pregnancy. *Epidemiology* 1999;10:112-7.
86. Tielemans E, Burdorf A, te Velde ER, Weber RF, van Kooij RJ, Veulemans H, et al. Occupationally related exposures and reduced semen quality: a case-control study. *Fertil Steril* 1999;71:690-6.
87. Tielemans E, van Kooij R, Looman C, Burdorf A, te Velde E, Heederik D. Paternal occupational exposures and embryo implantation rates after IVF. *Fertil Steril* 2000;74:690-5.
88. Smith EM, Hammonds-Ehlers M, Clark MK, Kirchner HL, Fuortes L. Occupational exposures and risk of female infertility. *J Occup Environ Med* 1997;39:138-47.
89. Tomenson JA, Taves DR, Cockett AT, McCusker J, Barraj L, Francis M, et al. An assessment of fertility in male workers exposed to molinate. *J Occup Environ Med* 1999;41:771-87.
90. Abell A, Ernst E, Bonde JP. Semen quality and sexual hormones in greenhouse workers. *Scand J Work Environ Health* 2000;26:492-500.
91. Harkonen K, Viitanen T, Larsen SB, Bonde JP, Lahdetie J. Aneuploidy in sperm and exposure to fungicides and lifestyle factors. *Environ Mol Mutagen* 1999;34:39-46.
92. Larsen SB, Spano M, Giwercman A, Bonde J. Semen quality and sex hormones among organic traditional Danish farmers. AESCEPIOS Study Group. *Occup Environ Med* 1999;56:1139-44.

ED_001854_00010739-00008

93. Potashnik G, Porath A. Dibromochloropropane (DBCP): a 17-year reassessment of testicular function and reproductive performance. *J Occup Environ Med* 1995;37:1287-92.
94. Recio R, Robbins WA, Borja-Aburto V, Moran-Martinez J, Froines JR, Hernandez RM et al. Organophosphorous pesticide exposure increases the frequency of sperm sex null aneuploidy. *Environ Health Perspect* 2001;109:1237-40.
95. Oliva A, Giami A, Multigner L. Environmental agents and erectile dysfunction: a study in a consulting population. *J Androl* 2002;23:546-50.
96. Oliva A, Spira A, Multigner L. Contribution of environmental factors to the risk of male infertility. *Hum Reprod* 2001;16:1768-76.
97. Padungtod C, Hassold TJ, Millie E, Ryan LM, Savitz DA, Christinani DC, et al. Sperm aneuploidy among Chinese pesticide factory workers: scoring by the FISH method. *Am J Ind Med* 1999;36:230-8.
98. Greenlee AR, Arbuckle TE, Chyou PH. Risk factors for female infertility in an agricultural region. *Epidemiology* 2003;14:429-36.
99. Heacock H, Hogg R, Marion SA, Hershler R, Teschke K, Dimich-Ward H, et al. Fertility among a cohort of male sawmill workers exposed to chlorophenate fungicides. *Epidemiology* 1998;9:56-60.
100. Barker D, Eriksson JG, Forsen T, Osmone D. Fetal origins of adult disease: strength of effect and biological basis. *Int J Epidemiol* 2002;31:1235-9.
101. Dabrowski S, Hanke W, Polanska K, Makowiec-Dabrowska T, Sobala W. Pesticide exposure and birthweight: an epidemiological study in Central Poland. *Int J Occup Med Environ Health* 2003;16:31-9.
102. Hanke W, Romitti P, Fuortes L, Sobala W, Mikulski M. The use of pesticides in a Polish rural population and its effect on birth weight. *Int Arch Occup Environ Health* 2003;76:614-20.
103. Hourani L, Hilton S. Occupational and environmental exposure correlates of adverse live-birth outcomes among 1032 US Navy women. *J Occup Environ Med* 2000;42:1156-65.
104. Karmaus W, Wolf N. Reduced birthweight and length in the offspring of females exposed to PCDFs, PCP, and lindane. *Environ Health Perspect* 1995;103:1120-5.
105. Kristensen P, Irgens LM, Andersen A, Bye AS, Sundheim L. Gestational age, birth weight, and perinatal death among births to Norwegian farmers, 1967-1991. *Am J Epidemiol* 1997;146:329-38.
106. Munger R, Isacson P, Hu S, Burns T, Hanson J, Lynch CF, et al. Intrauterine growth retardation in Iowa communities with herbicide-contaminated drinking water supplies. *Am J Epidemiol* 1997;105:308-14.
107. Levario-Carrillo M, Amato D, Ostrosky-Wegman P, Gonzalez-Horta C, Corona Y, Sanin LH. Relation between pesticide exposure and intrauterine growth retardation. *Chemosphere* 2004;55(10):1421-7.
108. Perera FP, Rauh V, Tsai WY, Kinney P, Camann D, Barr D, et al. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. *Environ Health Perspect* 2003;111:201-5.
109. Arbuckle TE, Lin Z, Mery LS. An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. *Environ Health Perspect* 2001;109:851-7.
110. Arbuckle TE, Savitz DA, Mery LS, Curtis KM. Exposure to phenoxy herbicides and the risk of spontaneous abortion. *Epidemiology* 1999;10:752-60.
111. Gerhard I, Daniel V, Link S, Monga B, Runnebaum B. Chlorinated hydrocarbons in women with repeated miscarriages. *Environ Health Perspect* 1998;106:675-81.
112. Jarrell J, Gocmen A, Foster W, Brant R, Chan S, Sevcik M. Evaluation of reproductive outcomes in women inadvertently exposed to hexachlorobenzene in southeastern Turkey in the 1950s. *Reprod Toxicol* 1998;12:469-76.
113. Petrelli G, Figa-Talamanca I, Tropeano R, Tangucci M, Cini C, Aquilani S, et al. Reproductive male-mediated risk: spontaneous abortion among wives of pesticide applicators. *Eur J Epidemiol* 2000;16:391-3.
114. Savitz DA, Arbuckle TE, Kaczor D, Curtis KM. Male pesticide exposure and pregnancy outcome. *Am J Epidemiol* 1997;146:1025-36.
115. Bell EM, Hertz-Picciotto I, Beaumont JJ. Case-cohort analysis of agricultural pesticide applications near maternal residence and selected causes of fetal death. *Am J Epidemiol* 2001;154:702-10.
116. Pastore LM, Hertz-Picciotto I, Beaumont JJ. Risk of stillbirth from occupational and residential exposures. *Occup Environ Med* 1997;54:511-8.
117. Gerhard I, Frick A, Monga B, Runnebaum B. Pentachlorophenol exposure in women with gynecological and endocrine dysfunction. *Environ Res* 1999;80:383-8.
118. Levario-Carrillo M, Feria-Velasco A, De Celis R, Ramos-Martinez E, Cordova-Fierro L, Solis FJ. Parathion, a cholinesterase-inhibiting pesticide induces changes in tertiary villi of placenta of women exposed: a scanning electron microscopy study. *Gynecol Obstet Invest* 2001;52:269-75.
119. Jarrell JF, Gocmen A, Akyol D, Brant R. Hexachlorobenzene exposure and the proportion of male births in Turkey 1935-1990. *Reprod Toxicol* 2002;16:65-70.
120. McGready R, Simpson JA, Htway M, White NJ, Nosten F, Lindsay SW. A double blind randomized therapeutic trial of insect repellents for the prevention of malaria in pregnancy. *Trans R Soc Trop Med Hyg* 2001;95:137-8.
121. Zeljezic D, Garaj-Vrhovac V. Chromosomal aberration and single cell gel electrophoresis (Comet) assay in the longitudinal risk assessment of occupational exposure to pesticides. *Mutagenesis* 2001;16:359-63.
122. Hagmar L, Bonassi S, Stromberg U, Brogger A, Knudsen LE, Norpa H, et al. Chromosomal aberrations in lymphocytes predict human cancer. *Cancer Res* 1998;58:4117-21.
123. Antonucci GA, de Syllos Colus IM. Chromosomal aberrations analysis in a Brazilian population exposed to pesticides. *Teratogen Carcinogen Mutagen* 2000;20:265-72.
124. Au WW, Sierra-Torres CH, Cajas-Salazar N, Shipp BK, Legator MS. Cytogenetic effects from exposure to mixed pesticides and the influence from genetic susceptibility. *Environ Health Perspect* 1999;107;501-55.
125. Carbonell E, Xamena N, Creus A, Marcos R. Cytogenetic biomonitoring in a Spanish group of agricultural workers exposed to pesticides. *Mutagenesis* 1993;8:511-7.
126. Carbonell E, Valbuena A, Xamena N, Creus A, Marcos R. Temporary variations in chromosomal aberrations in a group of agricultural workers exposed to pesticides. *Mutation Res* 1995;344:127-34.
127. Garaj-Vrhovac V, Zeljezic D. Assessment of genome damage in a population of Croatian workers employed in pesticide production by chromosomal aberration analysis, micronucleus assay and Comet assay. *J Appl Toxicol* 2002;22:249-55.
128. Gregio D'Arce LP, Colus IM. Cytogenetic and molecular biomonitoring of agricultural workers exposed to pesticides in Brazil. *Teratogen Carcinogen Mutagen* 2000;20:161-70.
129. Hoyos LS, Carvajal S, Solano L, Rodriguez J, Orozco L, Lopez Y, et al. Cytogenetic monitoring of farmers exposed to pesticides in Colombia. *Environ Health Perspect* 1996;104(Suppl 3):535-8.
130. Joksic G, Vidakovic A, Spasojevic-Tisma V. Cytogenetic monitoring of pesticide sprayers. *Environ Res* 1997;75:113-8.
131. Kaioumova DF, Khabutdinova LK. Cytogenetic characteristics of herbicide production workers in Ufa. *Chemosphere* 1998;37:1755-9.
132. Kourakis A, Mouratidou M, Barbouti A, Dimikiotou M. Cytogenetic effects of occupational exposure in the peripheral blood lymphocytes of pesticide sprayers. *Carcinogenesis* 1996;17:99-101.
133. Lander BF, Knudsen LE, Gamborg MO, Jarventaus H, Norppa H. Chromosome aberrations in pesticide-exposed greenhouse workers. Scand *J Work Environ Health* 2000;26:436-42.
134. Mohammad O, Walid AA, Ghada K. Chromosomal aberrations in human lymphocytes from two groups of workers occupationally exposed to pesticides in Syria. *Environ Res* 1995;70:24-9.
135. Paz-y-Mino C, Bustamante G, Sanchez ME, Leone PE. Cytogenetic monitoring in a population occupationally exposed to pesticides in Ecuador. *Environ Health Perspect* 2002;110:1077-80.
136. Varona M, Cardenas O, Crane C, Rocha S, Cuervo G, Vargas J. Cytogenetic alterations in workers exposed to pesticides in floriculture in Bogota [Spanish]. *Biomedica* 2003;23:141-52.
137. Bolognesi C. Genotoxicity of pesticides: a review of human biomonitoring studies. *Mutation Res* 2003;543:251-72.
138. Colosio C, Tiramani M, Maroni M. Neurobehavioral effects of pesticides: state of the art. *Neurotoxicology* 2003;24:577-91.
139. Whyatt RM, Rauh V, Barr DB, Camann DE, Andrews HF, Garfinkel R, et al. Prenatal insecticide exposures and birth weight and length among an urban minority cohort. *Environ Health Perspect* 2004;112:1125-32.
140. Williams MK, Barr DB, Camann DE, Cruz LA, Carlton EJ, Borjas M, et al. An intervention to reduce residential insecticide exposure during pregnancy. *Environ Health Perspect* 2006;114(11):1684-9.
141. Evans WE, McLeod HL. Pharmacogenomics—drug disposition, drug targets, and side effects. *N Engl J Med* 2003;348(6):538-49.
142. Berkowitz GS, Wetmur JG, Birman-Deych E, Obel J, Lapinski RH, Godbold JH, et al. In utero pesticide exposure, maternal paraoxanase activity and head circumference. *Environ Health Perspect* 2004;112(3):388-91.
143. Pesticide Free Ontario, Canadian Association of Physicians for the Environment, Oracle Poll. *Survey report.* Toronto, ON: Oracle Poll; 2007. Available from: **www.flora.org/healthyottawa/PFO%20CAPE%20Ont%20Poll%202007.pdf**. Accessed 2007 September 13.
144. Canadian Association of Physicians for the Environment. *CAPE position statement on pesticides.* Toronto, Ont: Canadian Association of Physicians for the Environment; 2000. Available from: **http://www.cape.ca/toxics/pesticidesps.html**. Accessed 2007 August 7.
145. Sear M, Walker CR, van der Jagt RH, Claman P. Pesticide assessment: protecting public health on the home turf. *Pediatr Child Health* 2006;11(4):229-34.
146. Buka I, Rogers WT, Osornio-Vargas AR, Hoffman H, Pearce M, Li YY. Parents and professionals ranked pesticides in water as an environmental concern second only to ETS. *Pediatr Child Health* 2006;11(4):235-8.
147. Arya N. Pesticides and human health: why public health officials should support a ban on non-essential residential use. *Can J Public Health* 2005;96(2):89-92.
148. American Academy of Pediatrics Committee on Environmental Health. Pesticides. In: Etzel RA, editor. *Pediatric environmental health.* 2nd ed. Elk Grove Village Ill: American Academy of Pediatrics; 2003. p. 323-59.
149. Ontario College of Family Physicians. Pesticides and your health.... Information from your family doctor [patient information brochure]. Toronto, Ont: Ontario College of Family Physicians; 2006. Available from: **www.ocfp.on.ca/local/files/EHC/Pesticide%20brochure.pdf**. Accessed 2007 August 7.
150. Marshall L, Weir E, Abelsohn A, Sanborn M. Identifying and managing environmental health effects: taking an exposure history. *CMAJ* 2002;166:1049-55.
151. Lessenger JE. Fifteen years of experience in cholinesterase monitoring of insecticide applicators. *J Agromed* 2005;10(3):49-56.
152. Mandel JH, Carr WP, Hillmer T, Leonard PR, Halberg JU, Sanderson WT, et al. Factors associated with safe use of agricultural pesticides in *Minnesota.J Rural Health* 1996;12(4 Suppl):301-10.
153. Keifer MC. Effectiveness of interventions in reducing pesticide overexposure and poisonings. *Am J Prev Med* 2000;18(4 Suppl):80-9.

ED_001854_00010739-00009

Review TRENDS in Cognitive Sciences Vol.9 No.2 February 2005

Full text provided by www.sciencedirect.com
SCIENCE DIRECT

Cognitive and affective development in adolescence

Laurence Steinberg

Department of Psychology, Temple University, Philadelphia, PA 19122, USA

Questions about the nature of normative and atypical development in adolescence have taken on special significance in the last few years, as scientists have begun to recast old portraits of adolescent behavior in the light of new knowledge about brain development. Adolescence is often a period of especially heightened vulnerability as a consequence of potential disjunctions between developing brain, behavioral and cognitive systems that mature along different timetables and under the control of both common and independent biological processes. Taken together, these developments reinforce the emerging understanding of adolescence as a critical or sensitive period for a reorganization of regulatory systems, a reorganization that is fraught with both risks and opportunities.

Introduction

Adolescence is characterized by an increased need to regulate affect and behavior in accordance with long-term goals and consequences, often at a distance from the adults who provided regulatory structure and guidance during childhood. Because developing brain, behavioral and cognitive systems mature at different rates and under the control of both common and independent biological processes, this period is often one of increased vulnerability and adjustment. Accordingly, normative development in adolescence can profitably be understood with respect to the coordination of emotional, intellectual and behavioral proclivities and capabilities, and psychopathology in adolescence may be reflective of difficulties in this coordination process.

The notion that adolescence is a heightened period of vulnerability specifically because of gaps between emotion, cognition and behavior has important implications for our understanding of many aspects of both normative and atypical development during this period of the life-span. With respect to normative development, for instance, this framework is helpful in understanding age differences in judgment and decision-making, in risk-taking, and in sensation-seeking [1]. With respect to atypical development, the framework helps us to understand why adolescence can be a time of increased risk for the onset of a wide range of emotional and behavioral problems, including depression, violent delinquency and substance abuse [2].

Corresponding author: Steinberg, L. (lds@temple.edu).
Available online 23 December 2004

Questions about the nature of normative and atypical development in adolescence have taken on special significance in the last few years as scientists have begun to recast old portraits of adolescent psychological development in light of new knowledge about adolescent brain development. Recent discoveries in the area of developmental neuroscience have stimulated widespread scientific and popular interest in the study of brain development during adolescence, as well as substantial speculation about the connections between brain maturation and adolescents' behavioral and emotional development. Indeed, the topic has garnered such widespread public interest that it was the subject of a recent cover story in *Time* magazine aimed at parents of teenagers [3], and was raised in arguments submitted in late 2004 to the United States Supreme Court in connection with the Court's consideration of the constitutionality of the juvenile death penalty [4].

Brain development in adolescence

As reviewed in the accompanying article by Paus [5] there is growing evidence that maturational brain processes are continuing well through adolescence. Even relatively simple structural measures, such as the ratio of white-to-gray matter in the brain, demonstrate large-scale changes into the late teen-age years [6–8]. The impact of this continued maturation on emotional, intellectual and behavioral development has yet to be thoroughly studied, but there is considerable evidence that the second decade of life is a period of great activity with respect to changes in brain structure and function, especially in regions and systems associated with response inhibition, the calibration of risk and reward, and emotion regulation. Contrary to earlier beliefs about brain maturation in adolescence, this activity is not limited to the early adolescent period, nor is it invariably linked to processes of pubertal maturation (Figure 1).

Two particular observations about brain development in adolescence are especially pertinent to our understanding of psychological development during this period. First, much brain development during adolescence is in the particular brain regions and systems that are key to the regulation of behavior and emotion and to the perception and evaluation of risk and reward. Second, it appears that changes in arousal and motivation brought on by pubertal maturation precede the development of regulatory competence in a manner that creates a disjunction between the adolescent's affective experience

www.sciencedirect.com 1364-6613/$ - see front matter © 2004 Elsevier Ltd. All rights reserved. doi:10.1016/j.tics.2004.12.005

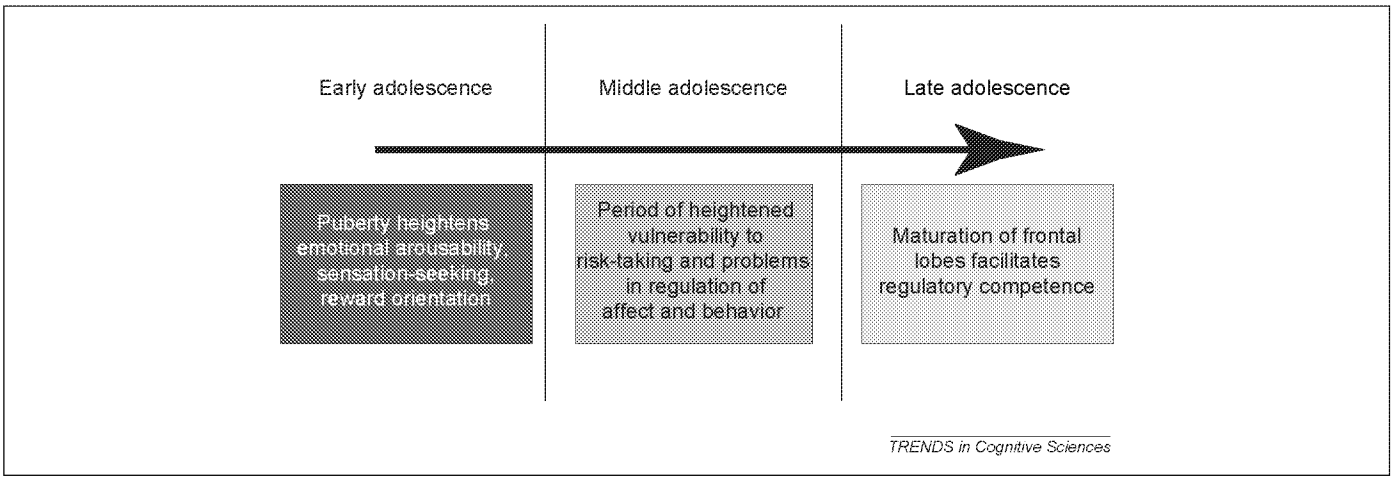


Figure 1. It has been speculated that the impact of puberty on arousal and motivation occurs before the maturation of the frontal lobes is complete. This gap may create a period of heightened vulnerability to problems in the regulation of affect and behavior, which might help to explain the increased potential in adolescence for risk-taking, recklessness, and the onset of emotional and behavioral problems.

and his or her ability to regulate arousal and motivation. To the extent that the changes in arousal and motivation precede the development of regulatory competence – a reasonable speculation, but one that has yet to be confirmed – the developments of early adolescence may well create a situation in which one is starting an engine without yet having a skilled driver behind the wheel [9].

Cognitive development in adolescence

Until recently, much of the work on adolescent cognitive development was devoted to a search for a core mechanism that could account parsimoniously for broad changes in adolescent thinking [10]. After nearly 50 years of searching, what has emerged instead is the necessity of an integrated account. What lies at the core of adolescent cognitive development is the attainment of a more fully conscious, self-directed and self-regulating mind [10]. This is achieved principally through the assembly of an advanced 'executive suite' of capabilities [11], rather than through specific advancement in any one of the constituent elements. This represents a major shift in prevailing views of adolescent cognition, going beyond the search for underlying elements [12] that are formed and operate largely outside awareness.

As Keating [10] has noted, the plausibility of such an integrative account has been substantially enhanced by recent major advances in the neurosciences [6–8,13–18], in comparative neuroanatomy across closely related primate species that illuminate core issues of human cognitive evolution [10,19], and in a deepened understanding of the critical role of culture and context in the shaping of cognitive and brain development [11,20]. Much of the underlying action is focused on specific developments in the prefrontal cortex, but with an equally significant role for rapidly expanding linkages to the whole brain [11,15,21]. This complex process of assembly is supported by increasingly rapid connectivity (through continued myelination of nerve fibers), particularly in communication among different brain regions, and by significant and localized synaptic pruning, especially in frontal areas that are crucial to executive functioning [6–8,18].

Whatever the underlying processes, during early adolescence, individuals show marked improvements in reasoning (especially deductive reasoning), information processing (in both efficiency and capacity), and expertise. These conclusions derive from studies of age differences in logical reasoning on tasks in which participants are asked to solve verbal analogies or analyze logical propositions; basic cognitive processes, such short- or long-term memory; and in specialized knowledge [10]. There has been broad consensus for more than 25 years that, as a result of these gains, individuals become more capable of abstract, multidimensional, planned and hypothetical thinking as they develop from late childhood into middle adolescence (less is known about cognitive changes during late adolescence). No research in the past several decades has challenge this conclusion.

Implications of new brain maturation research for adolescent cognitive development

After a rather lengthy period during the late 1980s and early 1990s, when the study of adolescent cognitive development was more or less moribund, interest in intellectual development during adolescence has been revitalized in recent years in two ways. First, researchers in the field of developmental neuroscience began to direct attention to the study of structural and functional aspects of brain development during early adolescence [6,8,13,22]. These studies have pointed both to significant growth and significant change in multiple regions of the prefrontal cortex throughout the course of adolescence, especially with respect to processes of myelination and synaptic pruning (both of which increase the efficiency of information processing) [8,17,23]. These changes are believed to undergird improvements in various aspects of executive functioning, including long-term planning, metacognition, self-evaluation, self-regulation and the coordination of affect and cognition [10]. Most research has focused on age differences in skills known to be related to functioning in the dorsolateral region of the prefrontal cortex, such as those involving working memory, spatial working memory and planning [24–26], but two recent studies [27,28] indicate as well that adolescence is a time of improvement

ED_001854_00010740-00002

in abilities that have been linked to functioning in the ventromedial prefrontal cortex, such as the calibration of risk and reward (Box 1).

In addition, adolescence appears to be a time of improved connectivity between regions of the prefrontal cortex and several areas of the limbic system, a restructuring that further affects the ways in which individuals evaluate and respond to risk and reward [22,29]. Whether and to what extent these changes in brain structure and function are linked to processes of pubertal maturation is not known. Some aspects of brain development are coincident with, and likely linked to, neuroendocrinological changes occurring at the time of puberty, but others appear to take place along a different, and later, timetable. Disentangling the first set from the second is an important challenge for the field [9]. It is also important to note that there are relatively few studies of developmental changes in brain function (as opposed to structure) in adolescence, and that conclusions about the putative links between changes in cognitive performance and changes in brain structure during adolescence are suggestive, rather than conclusive.

Box 1. Age differences in ventromedial functioning

The most widely used task in the assessment of ventromedial functioning is the Iowa Gambling Task [56]. Subjects are asked to draw cards from one of four face-down decks; each card provides information on how much has been won and lost on that draw. Cards from two of the decks offer high rewards, but in one deck the rewards are paired either with occasional very high losses, and in the other with frequent modest losses, and continuing to draw from either of these decks results in a net loss over time. By contrast, cards from the other two decks offer low rewards, but these are paired either with frequent small losses, or sporadic, but modest, losses, and these decks lead to net gains over time.

Researchers monitor individuals' pattern of card selection over numerous trials. Healthy adults typically begin by drawing from the decks at random, then gradually increase their pulls from the 'good' decks and decrease their pulls from the 'bad' decks. The notable exceptions to this pattern are patients with lesions to the ventromedial prefrontal cortex, individuals with substance abuse problems, and individuals who report high levels of risk-taking in everyday life, all of whom persist in drawing from the 'bad' decks despite the net losses that result.

Only recently have studies examined age differences on the Iowa Gambling Task. In one study [27] of four age groups – 6–9 year-olds, 10–12 year-olds, 13–15 year-olds and 18–25 year-olds – the youngest subjects drew equally from the good and bad decks. The two middle groups showed modest improvement over time; by the final trial block, they were drawing from the good decks about 55% and 60% of the time, respectively. By the final block, however, the young adults were drawing from the good deck nearly 75% of the time, and they began shifting towards the good decks much earlier than the younger groups.

Another study, of 9- to 17-year-olds, also found significant improvement in performance on this task with age [28]. 14–17 year-olds drew from the good decks more often than 9–10 year-olds (although not more often than 11–13 year olds) and began shifting to the good decks earlier than did either of the younger groups. The researchers also administered two tasks known to activate the dorsolateral prefrontal cortex: a go/no-go task, which assesses response inhibition, and a digit span test, which assesses working memory. As expected, performance on both dorsolateral tasks improved with age. More importantly, however, there were no significant correlations between performance on the ventromedial task and performance on either of the dorsolateral tasks, suggesting that maturation of the ventromedial prefrontal cortex may be a developmentally distinct process from the maturation of other regions of the frontal lobe.

Cognitive development in context

A second relatively new direction in research on adolescent cognitive development has involved the study of cognitive development as it plays out in its social context and, in particular, as it affects the development of judgment, decision-making and risk-taking [30–35]. New perspectives on adolescent cognition-in-context emphasize that adolescent thinking in the real world is a function of social and emotional, as well as cognitive, processes, and that a full account of the ways in which the intellectual changes of adolescence affect social and emotional development must examine the ways in which affect and cognition interact [10]. Studies of adolescents' reasoning or problem-solving using laboratory-based measures of intellectual functioning might provide better understanding of adolescents' potential competence than of their actual performance in everyday settings, where judgment and decision-making are likely affected by emotional states, social influences and expertise [1]. Thus, whereas studies of people's responses to hypothetical dilemmas involving the perception and appraisal of risk show few reliable age differences after middle adolescence, studies of actual risk-taking (e.g. risky driving, unprotected sexual activity, etc.) indicate that adolescents are significantly more likely to make risky decisions than are adults.

One reasonable hypothesis is that adults and adolescents 16 and older share the same logical competencies, but that age differences in social and emotional factors, such as susceptibility to peer influence or impulse control, lead to age differences in actual decision-making [36]. Research that examines developmental changes in cognitive abilities assessed under varying social and emotional conditions (e.g. the same task administered under conditions of high versus low affective arousal, or in the presence versus absence of peers) would be potentially quite informative, as at least one study indicates that adolescents' risk taking is more influenced than that of adults by the presence of peers [37] (Figure 2).

Consistent with findings on the advances in reasoning, characteristic of the transition into adolescence, studies of social cognition demonstrate that the ways in which adolescents think about others becomes more abstract, more differentiated and more multidimensional [38]. More recent studies of changes in social cognition during adolescence have attempted to clarify the conditions under which relatively more advanced displays of social cognition are likely to be seen; to describe gender and cultural differences in certain aspects of social cognition, such as prosocial reasoning [39,40] or impression formation [41]; and to examine the links between social cognition and social behavior. These studies indicate that patterns of social cognitive development in adolescence, like patterns of cognitive development more generally, vary both as a function of the content under consideration and the emotional and social context in which the reasoning occurs [38].

For example, although individuals' thinking about moral dilemmas becomes more principled over the course

ED_001854_00010740-00003

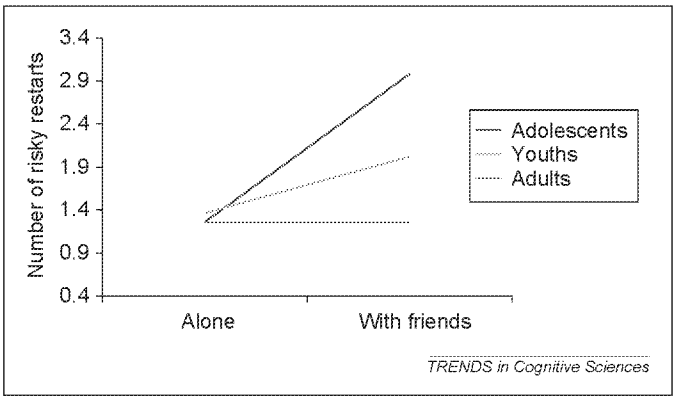


Figure 2. In a study designed to investigate age differences in risk-taking [37], participants were asked to play a computerized game in which they had opportunities to take driving risks, such as continuing to drive after a traffic light had turned yellow in order to drive the car further and earn more points. Individuals were randomly assigned to one of two conditions: playing the game alone, or playing it while two friends were watching and giving advice. The graph shows the number of times individuals risked crashing the car by stopping and then restarting it to try to drive a bit further after the yellow light had appeared. Adolescents (aged 13–16), youths (aged 18–22), and adults (aged 24 and older) demonstrated equivalent degrees of risk-taking when alone, but in the presence of peers, adolescents and youths, but not adults, took more risks.

of adolescence, their reasoning about real-life problems is often not as advanced as their reasoning about hypothetical dilemmas [42]. The correlation between adolescents' moral reasoning and their moral behavior is especially likely to break down when individuals define issues as personal choices rather than ethical dilemmas (for instance, when using drugs is seen as a personal matter rather than a moral issue) [43]. Similarly, when faced with a logical argument, adolescents are more likely to accept faulty reasoning or shaky evidence when they agree with the substance of the argument than when they do not [44,45]. And, although individuals' ability to look at things from another person's perspective increases in adolescence, the extent to which this advanced social perspective taking translates into tolerance for others' viewpoints depends on the particular issue involved [46]. In other words, adolescents' social reasoning, like that of adults, is influenced not only by their basic intellectual abilities, but by their desires, motives and interests.

Affect and cognition

In contrast to most measures of cognitive development in adolescence, which seem to correlate more closely with age and experience rather than the timing of pubertal maturation, there is evidence for a specific link between pubertal maturation and developmental changes in arousal, motivation and emotion. For example, there is evidence that pubertal development directly influences the development of romantic interest and sexual motivation [47,48]. There is also evidence that some changes in emotional intensity and reactivity, such as changes in the frequency and intensity of parent-adolescent conflict, may be more closely linked to pubertal maturation than to age [49]. Some cognitive skills related to human face-processing have also shown intriguing alterations in mid-adolescence – an apparent *decrement* in face processing skills that is associated with sexual maturation (measured by Tanner staging by physical examinations) rather than with age or grade level [50]. A parallel finding has been reported for voice recognition [51].

There is also evidence that increases in sensation-seeking, risk-taking and reckless behavior in adolescence are influenced by puberty and not chronological age. For example, in a study by Martin *et al.* [29], where sensation-seeking and risk behaviors were examined in a large group of young adolescents aged 11 to 14, there was no significant correlation between age and sensation-seeking, but a significant correlation between sensation-seeking and pubertal stage. There is also evidence in animal and human studies supporting a link between increasing levels of reproductive hormones and sensitivity to social status [52,53], which is consistent with the link between puberty and risk-taking, since several influential theories of adolescent risk-taking [54] suggest that at least some of this behavior is done in the service of enhancing one's standing with peers. Although further research is much needed, it appears that there are important links between pubertal maturation and social information-processing.

In some models of the development of affect regulation there is an explicit emphasis on cognitive systems exerting control over emotions and emotion-related behavior [55]. Many aspects of affect regulation involve the ability to inhibit, delay or modify an emotion or its expression in accordance with some rules, goals or strategies, or to avoid learned negative consequences. However, there is increasing understanding that cognitive-emotional interactions in adolescence also unfold in the other direction in important ways. Thus, just as cognition has an important impact on emotion, emotion has an important impact on basic cognitive processes, including decision-making and behavioral choice.

Decision-making and risk-taking

Behavioral data have often made it appear that adolescents are poor decision-makers (i.e. their high-rates of participation in dangerous activities, automobile accidents, drug use and unprotected sex). This led initially to hypotheses that adolescents had poor cognitive skills relevant to decision-making or that information about consequences of risky behavior may have been unclear to them [56,57]. In contrast to those accounts, however, there is substantial evidence that adolescents engage in dangerous activities *despite* knowing and understanding the risks involved [29,58,59,60–63]. Thus, in real-life situations, adolescents do not simply rationally weigh the relative risks and consequences of their behavior – their actions are largely influenced by feelings and social influences [1].

In contrast to much previous work on adolescent decision-making that emphasized cognitive processes and mainly ignored affective ones, there is now increasing recognition of the importance of emotion in decision-making [64]. The 'decision' to engage in a specific behavior with long-term health consequences – such as smoking a cigarette, drinking alcohol, or engaging in unprotected sex – cannot be completely understood within the framework of 'cold' cognitive processes. ('Cold' cognition refers to thinking processes under conditions of low emotion and/or arousal whereas 'hot' cognition refers to thinking under conditions of strong feelings or high arousal and which

ED_001854_00010740-00004

therefore may be much more important to understanding risky choices in real-life situations.) These affective influences are relevant in many day-to-day 'decisions' that are made at the level of 'gut-feelings' regarding what to do in a particular situation (rather than deliberate thoughts about outcome probabilities or risk value). These 'gut feelings' appear to be the products of affective systems in the brain that are performing computations that are largely outside conscious awareness [65,66]. How these feelings develop, become calibrated during maturation, and are influenced by particular types of experiences at particular points in development are only beginning to be studied within the framework of affective neuroscience [29]. It does, however, appear that puberty and sexual maturation have important influences on at least some aspects of affective influences on behavior through new drives, motivations and intensity of feelings, as well as new experiences that evoke strong feelings (such as developing romantic involvement) [67,68].

The development of regulatory competence

During the adolescent transition, regulatory systems are gradually brought under the control of central executive functions, with a special focus on the interface of cognition and emotion. Two important observations are especially important. The first is that the development of an integrated and consciously controlled 'executive suite' of regulatory capacities is a lengthy process. Yet, adolescents confront major, emotionally laden life dilemmas from a relatively early age – an age that has become progressively younger over historic time due to the decline in the age of pubertal onset and in the age at which a wide range of choices are thrust upon young people, as well as a decline in the active monitoring of adolescents by parents as a result of changes in family composition and labor force participation.

The second observation is that the acquisition of a fully coordinated and controlled set of executive functions occurs relatively later in development [10]. As such, it is less likely to be canalized (to the same degree as, say, early language acquisition), leaving greater opportunities for suboptimal trajectories. These suboptimal patterns of development take many different forms, clusters of which are associated with broad categories of psychopathology, such as the excessive down-regulation of mood and motivation that characterizes many internalizing difficulties, or the inadequate control of arousal that is associated with a wide range of risky behaviors typically seen as externalizing problems.

Concluding comments

Like early childhood, adolescence may well be a sensitive or critical developmental period for both normative and maladaptive patterns of development [69–71]. Several aspects of development during this period are especially significant in this regard, among them: the role of puberty in a fundamental restructuring of many body systems and as an influence on social information-processing; the apparent concentration of changes in the adolescent brain in the prefrontal cortex (which serves as a governor of cognition and action) together with the enhanced inter-regional communication between the prefrontal cortex and other brain regions; and the evidence for substantial synaptic pruning and for non-trivial physiological reversibility of behavioral and neuroendocrine patterns arising from early developmental experiences. Taken together, these developments reinforce the emerging understanding of adolescence as a critical or sensitive period for a reorganization of regulatory systems, a reorganization that is fraught with both risks and opportunities [10]. As we look to the future of research on cognitive and affective development in adolescence, the challenge facing researchers will be integrating research on psychological, neuropsychological and neurobiological development. What we now have are interesting pieces of a complicated puzzle, but the pieces have yet to be fit together in a way that moves the field out of the realm of speculation and towards some measure of certainty.

Acknowledgements

Many of the ideas expressed in this article grew out of the work of the MacArthur Foundation Research Network on Psychopathology and Development. I am especially grateful to Ron Dahl, Dan Keating, David Kupfer, Ann Masten and Danny Pine for their contributions to the enterprise. Thanks also to Marnia Davis for bibliographic assistance.

References

1 Steinberg, L. (2004) Risk-taking in adolescence: What changes, and why? *Ann. N. Y. Acad. Sci.* 1021, 51–58
2 Steinberg, L. *et al.* Psychopathology in adolescence: Integrating affective neuroscience with the study of context. In *Developmental Psychopathology Vol. 1: Theory and Method* (Cicchetti, D. and Cohen, D., eds), Wiley (in press)
3 Wallis, C. (2004) What makes teens tick. *Time* 10 May, pp. 56–65
4 Wiener, R. and Miller, M. (2004) Determining the death penalty for juveniles. *APA Monitor on Psychology* 35, 68
5 Paus, T. (2005) Mapping brain maturation and cognitive development during adolescence. *Trends Cogn. Sci.* 9, 000–000
6 Giedd, J. *et al.* (1999) Brain development during childhood and adolescence: A longitudinal MRI study. *Nat. Neurosci.* 2, 861–863
7 Sowell, E.R. *et al.* (2001) Improved memory functioning and frontal lobe maturation between childhood and adolescence: A structural MRI study. *J. Int. Neuropsychol. Soc.* 7, 312–322
8 Sowell, E.R. *et al.* (2002) Development of cortical and subcortical brain structures in childhood and adolescence: A structural MRI study. *Dev. Med. Child Neurol.* 44, 4–16
9 Dahl, R.E. (2001) Affect regulation, brain development, and behavioral/emotional health in adolescence. *CNS Spectr.* 6, 1–12
10 Keating, D.P. (2004) Cognitive and brain development. In *Handbook of Adolescent Psychology* (2nd edn) (Lerner, R.J. and Steinberg, L.D., eds), pp. 45–84, Wiley
11 Donald, M. (2001) *A Mind So Rare: The Evolution of Human Consciousness*, Norton
12 Dennett, D.C. (1996) *Kinds of Minds: Toward an Understanding of Consciousness*, Basic Books
13 Casey, B.J. *et al.* (2000) Structural and functional brain development and its relation to cognitive development. *Biol. Psychol.* 54, 241–257
14 Johnson, M.H. (2001) Functional brain development in humans. *Nat. Rev. Neurosci.* 2, 475–483
15 Luna, B. *et al.* (2001) Maturation of widely distributed brain function subserves cognitive development. *Neuroimage* 13, 786–793
16 Nelson, C.A. (1999) Neural plasticity and human development. *Curr. Dir. Psychol. Sci.* 8, 42–45
17 Paus, T. *et al.* (1999) Structural maturation of neural pathways in children and adolescents: *in vivo* study. *Science* 283, 1908–1911
18 Steingard, R.J. *et al.* (2002) Smaller frontal lobe white matter volumes in depressed adolescents. *Biol. Psychiatry* 52, 413–417
19 Rilling, J.K. and Insel, T.R. (1999) The primate neocortex in comparative perspective using magnetic resonance imaging. *J. Hum. Evol.* 37, 191–223

ED_001854_00010740-00005

20 Francis, D.D. *et al.* (2002) Environmental enrichment reverses the effects of maternal separation on stress reactivity. *J. Neurosci.* 22, 7840–7843
21 Newman, J. and Grace, A.A. (1999) Binding across time: The selective gating of frontal and hippocampal systems modulating working memory and attentional states. *Conscious. Cogn.* 8, 196–212
22 Spear, P. (2000) The adolescent brain and age-related behavioral manifestations. *Neurosci. Biobehav. Rev.* 24, 417–463
23 Huttenlocher, P. (1994) Synaptogenesis, synapse elimination, and neural plticity in human cerebral cortex. In *Threats to Optimal Development: Integrating Biological, Psychological, and Social Risk Factors* (Vol. 27) (Nelson, C., ed.), pp. 35–54, Eralbaum
24 Luciana, M. and Nelson, C. (2002) Assessment of neuropsychological function through use of the Cambridge Neuropsychological Testing Automated Battery: Performance in 4- to 12-year-old children. *Dev. Neuropsychol.* 22, 595–624
25 Vuontella, V. *et al.* (2003) Audiospatial and visuospatial working memory in 6-13 year old school children. *Learn. Mem.* 10, 74–84
26 Welsh, M. *et al.* (1991) A normative-developmental study of executive function: A window on prefrontal function in children. *Dev. Neuropsychol.* 7, 131–149
27 Crone, E. and van der Molen, M. (2004) Developmental changes in real-life decision-making: Performance on a gambling task previously shown to depend on the ventromedial prefrontal cortex. *Dev. Neuropsychol.* 25, 251–279
28 Hooper, C. *et al.* (2004) Adolescents' performance on the Iowa Gabling Task: Implications for the development of decision-making and ventromedial prefrontal cortex. *Dev. Psychol.* 40, 1148–1158
29 Martin, C.A. *et al.* (2002) Sensation seeking, puberty and nicotine, alcohol and marijuana use in adolescence. *J. Am. Acad. Child Adolesc. Psychiatry* 41, 1495–1502
30 Cauffman, E. and Steinberg, L. (2000) (Im)maturity of judgment in adolescence: Why adolescents may be less culpable than adults. *Behav. Sci. Law* 18, 1–21
31 Fried, C.S. and Reppucci, N. (2001) Criminal decision-making: The development of adolescent judgment, criminal responsibility, and culpability. *Law Hum. Behav.* 25, 45–61
32 Maggs, J. *et al.* (1995) Risky business: The paradoxical meaning of problem behavior for young adolescents. *J. Early Adolesc.* 15, 344–362
33 Miller, D. and Byrnes, J. (1997) The role of contextual and personal factors in children's risk taking. *Dev. Psychol.* 33, 814–823
34 Scott, E. *et al.* (1995) Evaluating adolescent decision making in legal contexts. *Law Hum. Behav.* 19, 221–244
35 Steinberg, L. and Cauffman, E. (1996) Maturity of judgment in adolescence: Psychosocial factors in adolescent decisionmaking. *Law Hum. Behav.* 20, 249–272
36 Steinberg, L. *Adolescence* (7th edn), McGraw-Hill (in press)
37 Gardner, M. and Steinberg, L. Risk-taking among adolescents, young adults, and adults: The role of peer influence. *Dev. Psychol.* (in press)
38 Eisenberg, N. and Morris, A. (2004) Moral cognitions and prosocial responding in adolescence. In *Handbook of Adolescent Psychology* (Lerner, R. and Steinberg, L., eds), pp. 155–188, Wiley
39 Boehnke, K. *et al.* (1989) Developmental pattern of prosocial motivation: A cross national study. *J. Cross Cult. Psychol.* 20, 219–243
40 Jaffee, S. and Hyde, J.S. (2000) Gender differences in moral orientation: A meta-analysis. *Psychol. Bull.* 126, 703–726
41 Crystal, D. *et al.* (1998) Concepts of human differences: A comparison of American, Japanese, and Chinese children and adolescents. *Dev. Psychol.* 34, 714–722
42 Sobesky, W. (1983) The effects of situational factors on moral judgments. *Child Dev.* 54, 575–584
43 Kuther, T.L. and Higgins-D'Alessandro, A. (2000) Bridging the gap between moral reasoning and adolescent engagement in risky behavior. *J. Adolesc.* 23, 409–422
44 Klaczynski, P.A. (1997) Bias in adolescents' everyday reasoning and its relationships with intellectual ability, personal theories, and self-serving motivation. *Dev. Psychol.* 33, 273–283
45 Klaczynski, P. and Gordon, D. (1996) Everyday statistical reasoning during adolescence and young adulthood: Motivational, general ability, and developmental influences. *Child Dev.* 67, 2873–2891
46 Wainryb, C. *et al.* (2001) Children's, adolescents', and young adults' thinking about different types of disagreements. *Dev. Psychol.* 37, 373–386
47 Neeman, J. *et al.* (1995) The changing importance of romantic relationship involvement to competence from late childhood to late adolescence. *Dev. Psychopathol.* 7, 727–750
48 Udry, J. (1987) Hormonal and social determinants of adolescent sexual initiation. In *Adolescence and Puberty* (Bancroft, J., ed.), pp. 70–87, Oxford University Press
49 Steinberg, L. (1987) The impact of puberty on family relations: Effects of pubertal status and pubertal timing. *Dev. Psychol.* 23, 451–460
50 Diamond, R. *et al.* (1983) Genetic influences on the development of spatial skills during early adolescence. *Cognition* 13, 167–185
51 Mann, V. *et al.* (1979) Development of voice recognition: Parallels with face recognition. *J. Exp. Child Psychol.* 27, 153–165
52 Book, A. *et al.* (2001) The relationship between testosterone and aggression: A meta-analysis. *Aggression & Violent Behavior* 6, 579–599
53 Josephs, R.A. *et al.* (2003) Status, testosterone, and human intellectual performance: Stereotype threat as status concern. *Psychol. Sci.* 14, 158–163
54 Moffitt, T. (1993) Adolescence-limited and life-course-persistent antisocial behavior: A developmental taxonomy. *Psychol. Rev.* 100, 674–701
55 Thompson, R.A. and Fox, N.A. eds. (1994) Emotion regulation: A theme in search of definition. Monogr. Soc. Res. Child Dev. 59, No. 240
56 Botvin, G. (1991) Substance abuse prevention: Theory, practice, and effectiveness. In Crime and Justice (Tonry, M., ed.), pp. 461–519, University of Chicago Press
57 Tobler, N. (1986) Meta-analysis of 143 adolescent prevention programs: Quantitative outcome results of program participants compared to a control or comparison group. *J. Drug Issues* 16, 537–567
58 Benthin, A. *et al.* (1995) Adolescent health-threatening and health-enhancing behaviors: A study of word association and imagery. *J. Adolesc. Health* 17, 143–152
59 Cauffman, E. and Steinberg, L. (1995) The cognitive and affective influences on adolescent decision-making. *Temple Law Rev.* 68, 1763–1789
60 Slovic, P. (1987) Perception of risk. *Science* 236, 280–285
61 Slovic, P. (1998) Do adolescent smokers know the risks? *Duke Law J.* 47, 1133–1141
62 Slovic, P. (2000) What does it mean to know a cumulative risk? Adolescent's perceptions of short-term and long-term consequences of smoking. *J. Behav. Decis. Making* 13, 259–266
63 Slovic, P. (2000) Rejoinder: The perils of Viscusi's analyses of smoking risk perceptions. *J. Behav. Decis. Making* 13, 273–276
64 Loewenstein, G. and Lerner, J.S. The role of affect in decision-making. In *Handbook of Affective Science* (Goldsmith, H., ed.), Oxford University Press (in press)
65 Bechara, A. *et al.* (2000) Emotion, decision making and the orbitofrontal cortex. *Cereb. Cortex* 10, 295–307
66 Bechara, A. *et al.* (1999) Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *J. Neurosci.* 19, 5473–5481
67 Keating, D.P. and Sasse, D.K. (1996) Cognitive socialization in adolescence: Critical period for a critical habit of mind. In *Psychosocial Development During Adolescence: Progress in Developmental Contextualism* (Gullota, T.P., ed.), pp. 232–258, Sage
68 Richards, M.H. *et al.* (1998) Developmental patterns and gender differences in the experience of peer companionship during adolescence. *Child Dev.* 69, 154–163
69 Boyce, W.T. and Keating, D.P. Should we intervene to improve childhood circumstances? In *A Life Course Approach to Chronic Disease Epidemiology* (2nd edn) (Kuh, D. and Ben-Shlomo, Y., eds), Oxford University Press (in press)
70 Keating, D.P. and Hertzman, C. eds. (1999) *Developmental health and the wealth of nations: Social, biological, and educational dynamics*, Guilford Press
71 Meaney, M.J. (2001) Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annu. Rev. Neurosci.* 24, 1161–1192

ED_001854_00010740-00006

Springer

Maturity of Judgment in Adolescence: Psychosocial Factors in Adolescent Decision Making
Author(s): Laurence Steinberg and Elizabeth Cauffman
Source: *Law and Human Behavior*, Vol. 20, No. 3, Children's Capacities in Legal Contexts (Jun., 1996), pp. 249-272
Published by: Springer
Stable URL: http://www.jstor.org/stable/1393975
Accessed: 27-03-2017 16:29 UTC

REFERENCES
Linked references are available on JSTOR for this article:
http://www.jstor.org/stable/1393975?seq=1&cid=pdf-reference#references_tab_contents
You may need to log in to JSTOR to access the linked references.

JSTOR is a not-for-profit service that helps scholars, researchers, and students discover, use, and build upon a wide range of content in a trusted digital archive. We use information technology and tools to increase productivity and facilitate new forms of scholarship. For more information about JSTOR, please contact support@jstor.org.

Your use of the JSTOR archive indicates your acceptance of the Terms & Conditions of Use, available at
http://about.jstor.org/terms

Springer is collaborating with JSTOR to digitize, preserve and extend access to *Law and Human Behavior*

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

ED_001854_00010741-00001

Law and Human Behavior, Vol. 20, No. 3, 1996

Maturity of Judgment in Adolescence: Psychosocial Factors in Adolescent Decision Making

Laurence Steinberg[1] and Elizabeth Cauffman[1]

To date, analyses of differences between adolescents' and adults' judgment have emphasized age differences in cognitive factors presumed to affect decision making. In contrast, this article examines research and theory on three psychosocial *aspects of maturity of judgment: responsibility, temperance, and perspective. For several psychosocial dimensions of maturity that are likely to affect judgment, the existing evidence, while indirect and imperfect, indicates that the greatest differences are found in comparisons between early adolescents versus middle and late adolescents. Developmental research on maturity that focuses specifically on mid- and late adolescence, that simultaneously examines both cognitive and noncognitive factors, and that investigates the relation between these factors and the ability to make good decisions is greatly needed.*

The treatment of adolescents under the modern legal system often hinges on considerations of young people's psychological maturity, and on beliefs about the impact of maturity on judgment and decision making. During most of the past century, adolescents have been viewed under the law as immature and less capable than adults of acting in their own best interest. This dual proposition—that adolescents are psychologically less mature than adults, and that this immaturity impairs young people's judgment—is the focus of the present article.

Presumptions about the inherent immaturity of adolescents are numerous and pervasive within the law. Adolescents have been deemed unable to provide informed consent for most health care procedures (Gittler, Quigley-Rick, & Saks, 1990). Minors are allowed to enter contracts but may disavow them at any time; these contracts are not necessarily void but they are voidable by the minor, and a child is usually not liable for tortious breach of contract (Nurcombe & Partlett, 1994). The contemporary juvenile justice system is organized on the premises that (1) many transgressions committed by minors are the result of poor or immature

[1]To whom correspondence should be addressed at the Department of Psychology, Temple University, Philadelphia, PA 19122 (e-mail: LDS@VM.TEMPLE.EDU).

0147-7307/96/0600-0249$09.50/1 © 1996 American Psychology-Law Society/Division 41 of the American Psychological Association

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

ED_001854_00010741-00002

judgment, and (2) minors can be rehabilitated more easily than adults (i.e., that their character is less mature, or less fully formed) (Mack, 1909).

In recent years, the prevailing view of adolescents as inherently less mature than adults has been challenged on several fronts. Several recent empirical studies have called into question widely held presumptions about the differences between adolescents' and adults' thinking in decision making situations (e.g., Furby & Beyth-Marom, 1992). Public outrage over the surge in juvenile violence has provoked considerable debate about the practice of treating adolescents within a separate justice system. In discussions about a variety of health care issues, it increasingly has been argued that teenagers are sufficiently mature to provide informed consent, and several states have enacted statutes that authorize minors to consent for care or seek treatment without parental consent for problems related to sexual activity, drug and alcohol use, or psychological distress (Gittler, Quigley-Rick, & Saks, 1990). Given the widespread use of the construct of immaturity to distinguish between adolescents and adults under current law, and in light of growing questions about the wisdom of this practice, there is good reason to examine the relevant psychological evidence on the issue.

Accounts of adolescent immaturity may be classified into two broad categories: those attributed to cognitive differences between adolescents and adults (i.e., differences in the way they think), and those attributed to psychosocial differences (i.e., differences in their social and emotional maturity). These differences are assumed to reflect differences in competence due to differences in developmental status (independent of experience), differences in experience (independent of developmental status), or some combination of both.

To date, psychological investigations of adolescent immaturity within a legal context have emphasized cognitive factors, rather than emotional or social ones. This emphasis reflects the influence of the informed consent model on the analysis of legal issues concerning adolescents, since this model places a premium on factors such as "knowledge" and "competence" (Culver, 1982; Grisso & Vierling, 1978; Marks, 1975; Meisel, Roth, & Lidz, 1977; Murphy, 1979; Wadlington, 1983). Recently, however, it has been suggested that the informed consent model is too narrow in scope to adequately illuminate differences between adolescents' and adults' decision making, because it overemphasizes cognitive functioning (e.g., capacity for thinking, reasoning, understanding) and minimizes the importance of noncognitive, psychosocial, variables that influence the decision-making process (i.e., aspects of development and behavior that involve personality traits, interpersonal relations, and affective experience) (Scott, Reppucci, & Woolard, 1995). Scott et al. argued that there is more to competent decision making than cognitive competence and urged researchers to examine developmental aspects of "judgment," more broadly conceived.

In this review, we build on Scott et al.'s analysis and present a framework for research and theory about psychosocial aspects of, and influences on, maturity of judgment in adolescence. Our purpose is to draw together several potentially relevant literatures with the goal of stimulating the further development of theory and empirical research. In doing so, we shall raise questions about what it means to be psychosocially "mature," whether psychosocial maturity is in fact related to judg-

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

ED_001854_00010741-00003

ment or decision making, and whether observed differences in psychosocial maturity between adolescents and adults (or among adolescents of different ages) are sufficient to serve as a basis for drawing distinctions between these age groups in matters of law.

Like Scott et al. (1995), our position is that mature judgments are the product of an interaction between cognitive and psychosocial factors, with competent decision making potentially undermined by deficiencies in either domain. An individual facing a particular decision may have the cognitive skills to evaluate the costs and benefits of various courses of action, but if the individual is especially impulsive, he or she may not make a wise decision. By the same token, even the most responsible and temperate individual will not make competent decisions if he or she lacks the requisite cognitive skills or access to relevant information.

Although we shall attempt to maintain the distinction between psychosocial and cognitive aspects of maturity, the distinction is imperfect. A fair amount of research has looked at the relation between emotion and cognition, for example, examining how variations in emotional states (e.g., euphoria, depression, anxiety) affect decision making and judgment (for a review, see Mann, 1992). Other research has examined the link between interpersonal variables and cognition, as in Asch's classic studies of the influence of social pressure on object perception (Asch, 1955). To our knowledge, however, the links between cognitive and noncognitive factors have not been examined *developmentally* or with specific reference to adolescence. To the extent that the relation between emotion and cognition, or between social influence and cognition, changes with age (if, for example, younger individuals' decision making were more influenced by their emotions or by social influences than were the decision making of older individuals), investigating the psychosocial and cognitive aspects of maturity separately may lead to misleading conclusions about age differences in judgment. One of the most significant weaknesses in extant research on differences between adolescent and adult decision making is the failure of researchers to take into account possible links between emotion and cognition in situations calling for mature judgment.

A WORKING DEFINITION OF MATURITY OF JUDGMENT IN ADOLESCENCE

As important as the notion of "maturity" is in the treatment of adolescents under the law, it remains a remarkably elusive and ill-defined construct among legal scholars and social scientists. Sociologists define maturity as the end-product of "socialization." Psychologists have proposed similar definitions; Greenberger and Sorensen (1974), for example, define maturity as the capacity to function adequately on one's own, to contribute to social cohesion, and to interact adequately with others. Although useful starting points, in our view, such broad definitions of maturity are probably beyond what is necessary or feasible for the purposes of the law.

Because we are interested specifically in maturity of judgment, we emphasize in our model only those psychosocial factors that likely are relevant to decision making. While such factors are numerous, we posit that the vast majority of them

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

fall into one of three categories of overarching dispositions: (1) *responsibility* (i.e., healthy autonomy, self-reliance, and clarity of identity); (2) *temperance* (i.e., the ability to limit impulsivity, avoid extremes in decision making, and to evaluate a situation thoroughly before acting, including seeking the advice of others when appropriate); and (3) *perspective* (i.e., being able to acknowledge the complexity of a situation and to frame a specific decision within a larger context). When considered along with the cognitive competence to reason abstractly, these dispositions comprise the attributes most often associated with mature decision making in the literature on adolescent psychological development (cf. Greenberger & Sorensen, 1974; Irwin & Millstein, 1992).

Although we are attempting to formulate a general model of maturity of judgment that can be applied across a variety of situations, we recognize that whether an individual actually demonstrates responsibility, temperance, or perspective when faced with a particular decision likely depends on the nature of the situation and the social context of the decision. The same adolescent may in some situations behave responsibly, while in others, irresponsibly; show temperance under certain conditions but impulsively under others; and demonstrate perspective in some circumstances but short-sightedness in others. We believe therefore that responsibility, temperance, and perspective are best conceived as *dispositions* to behave in a given way *under particular conditions*, rather than as fixed abilities or competencies that are displayed independently of context. As ecologically oriented psychologists, we firmly believe that an individual's maturity of judgment must be evaluated in light of a particular decision and a specific situation. As developmental psychologists, however, we also believe that it is both possible and fruitful to ask whether there are developmental trends in maturity that may be informative to discussions of adolescent decision making across a variety of legal contexts.

Having sketched out a rudimentary working model of the construct of maturity, it is possible to formulate more specific empirical questions relevant to the task before us. Specifically, do adolescents and adults (or adolescents of different ages) differ in their disposition toward responsibility? In their disposition toward temperance? In their disposition to place things in perspective? If so, how do these differences manifest themselves in decision-making situations? Do these differences vary depending upon the context in which the decision is made? Are such differences appreciable and consistent enough to warrant the drawing of legal distinctions between adolescents and adults on the basis of differences in maturity? We begin with an examination of theory and research on the development of responsibility.

THE DEVELOPMENT OF RESPONSIBILITY

The study of responsibility in adolescence draws from several different perspectives on psychosocial development during the second decade of life. One school of thought emphasizes the adolescent's growing capacity for autonomy or independence. Another focuses on the adolescent's developing sense of identity. A third concerns "ego development"—which includes, among other related constructs, individuation (the development of a separate sense of self) and internalization (the

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

process through which the adolescent incorporates into his or her own personality the values, controls, and evaluations of parents and other adults who had been in positions of authority) (Josselson, 1980).

Autonomy and Independence

During the second decade of life, individuals become more capable of independent decision making, less easily influenced by the advice or urgings of others, and more able to function responsibly in the absence of adult supervision (Steinberg, 1990). Within the study of independence, researchers have focused mainly on the study of self-reliance and on susceptibility to social influence, especially, but not exclusively, the influence of peers (more popularly referred to as research on "peer pressure") (see also Scott et al., 1995). Self-reliance and related constructs, such as internal locus of control or self-efficacy, are typically studied via standardized personality instruments that assess the adolescent's capacity for independent behavior and decision making, and mature individuals are those who report strong feelings of internal (as opposed to external) control and the ability to make decisions without excessive reliance on others (Greenberger & Sorensen, 1974). Measures of susceptibility to social influence typically employ hypothetical dilemmas that place the adolescent between two opposing forces and ask the respondent to select one of two courses of action.

Early studies of adolescents' susceptibility to influence found that the salience of different types of social influence varied as a function of topic: Parents were found to be more influential in matters of religion, educational plans, occupational choice, or other "deep" issues, whereas peers were found to be more influential in day-to-day affairs, such as taste in clothing, music, and the like (Brittain, 1963). These studies remind us that adolescents' display of independence—and hence, maturity of judgment—may be highly situation-specific, with youngsters being influenced more on some topics than others, and by different sources of influence to different degrees, depending on the decision in question. In more recent decades, instruments assessing susceptibility to social influence have asked the adolescent to choose between giving into the wishes of others versus following his or her personal beliefs (e.g., Berndt, 1979). Maturity is defined as the ability to resist pressure from others to engage in behavior that is contrary to one's own wishes, and the most mature individuals are those who are the most free from social influence. As we shall see, this latter notion is based on a questionable premise.

Most research on adolescent autonomy has studied individual differences among same-aged youngsters. Fewer studies have examined age differences in either self-reliance or susceptibility to social influence, and these studies have tended to focus on age differences *within* the adolescent population, rather than differences between adolescents and adults. In general, studies of self-reliance show steady and gradual increases in youngsters' capacity for self-direction throughout the adolescent years, with gains continuing through the final years of high school (Greenberger, 1982). Susceptibility to parental influence follows a similar trend, with youngsters becoming less easily influenced by their parents with age (Berndt, 1979).

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

Interestingly, susceptibility to *peer* influence follows an inverted U-shaped function, increasing between childhood and early adolescence, peaking sometime around age 14, and declining during the early high school years (Steinberg & Silverberg, 1986). It is not clear whether this midadolescence increase in resistance to peer pressure reflects a growing capacity for self-direction or, as some theorists have suggested, a waning of the intensity of pressure that adolescents exert on each other (Brown, 1990). In either case, however, the evidence is that between the ages of 10 and 18, adolescents grow more able to make decisions on their own, and that sometime between the ages of 12 and 16, peer pressure begins to play a smaller role in adolescent decision making.

Missing from the literature on autonomy in adolescence are studies that explicitly examine the relation between judgment and either self-reliance or susceptibility to social influence. Although individuals who are more susceptible to pressure to engage in antisocial activities are in fact more likely to commit delinquent acts (Brown, 1990), we do not know whether individuals who are high in self-reliance or in their ability to resist peer pressure actually are more likely to make competent decisions. Overall, then, the link between psychosocial aspects of adolescent autonomy and judgment in real-life situations is in theory only. We do not know, therefore, whether observed age differences in autonomy are in fact correlated with age differences in maturity of judgment.

Measures of autonomy (whether defined as self-reliance or as invulnerability to social influence) place a premium on independent decision making that may underestimate the importance of advice seeking as a component of maturity of judgment. Healthy decision making is not equivalent to decision making that disregards the advice or expertise of others. Indeed, one of the hallmarks of mature judgment is knowing where to turn for advice, knowing how to solicit it, and knowing whether and to what extent to follow it. Unfortunately, research on advice seeking and expertise utilization in adolescence is sparse. In one widely cited study, older adolescents were better able than younger ones to look ahead and assess risks and likely outcomes of alternative choices, better able to recognize the value of turning to an independent "expert," and better able to see that someone's advice may be tainted by his or her own interests (Lewis, 1981). Because this study did not include young adults, however, we do not know if gains in this aspect of decision making continue to accrue after age 18.

Identity

A second perspective on the development of responsibility in adolescence emphasizes the development of a coherent sense of identity. Presumably, individuals who are confident, aware of their personal strengths and weaknesses, and clear about their values and priorities will exercise more mature judgment than those who are insecure, not especially self-aware, and confused about their beliefs. Because confidence, self-awareness, and clarification of values are all hypothesized to increase during adolescence, developments in the domain of identity may have implications for the growth of mature judgment.

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

The dominant theoretical framework in the study of adolescent identity development is that of Erik Erikson (1968). According to Erikson, adolescence is a time of role experimentation and exploration of the self, and it is through these processes that the adolescent establishes a coherent sense of identity—a sense of knowing who one is and where one is headed. From the Eriksonian vantage point, individuals would be unlikely to display mature judgment during the period of experimentation and exploration (a period known as the "psychosocial moratorium"), since a coherent sense of identity has not yet been established. Following the moratorium, however, if the identity crisis has been successfully resolved, the individual should enter into decision-making situations with greater confidence and clarity of insight.

We know of no work that has explicitly examined the relation between identity development and maturity of judgment, although there is indirect evidence to link the two. Adolescents categorized as having achieved a sense of identity score highest on measures of moral reasoning, reflectiveness, and career maturity, whereas individuals still in the midst of the moratorium score highest on measures of anxiety and show the highest levels of conflict over issues of authority. Individuals classified as having "foreclosed" the identity process have been shown to be the most authoritarian, to have the highest need for social approval, and to be lowest in self-reliance. Finally, individuals who suffer from "identity confusion" display a variety of psychological and interpersonal problems (Adams, Gullotta, & Montemayor, 1992; Wallace-Brosious, Serafica, & Osipow, 1994).

Because identity achievement is likely associated with maturity of judgment, studies of age differences in identity development are especially pertinent. Perhaps the most significant finding to emerge from this line of work is that establishing a coherent sense of identity generally does not occur much before age 18 (Marcia, 1980). In general, when comparisons are made among groups of youngsters of different ages over the span from ages 12 to 24, differences in identity development are most frequently observed between age groups within the 18- to 21-year-old range. Few consistent differences emerge in comparisons of teenagers in the middle adolescent years, suggesting that, although self-examination may take place throughout adolescence, the consolidation of a coherent sense of identity does not begin until the late teens or early twenties (Adams & Jones, 1983; Archer, 1982; Montemayor, Brown, & Adams, 1985). To the extent, then, that maturity of judgment goes hand in hand with consolidation of a sense of identity, research in the Eriksonian tradition suggests that most individuals would not be expected to display consistently mature judgment until the age of 18, at the earliest.

Researchers also have studied identity development by examining changes in individuals' self-evaluations during adolescence. Because individuals with low self-esteem or limited self-awareness may be hesitant in decision-making situations and likely to seek social approval rather than follow their best intuitions, research in changes in the self-image is relevant to the study of maturity. In theory, maturity of judgment should increase as individuals become more confident and self-assured.

The widely held characterization of adolescence as a time of extreme vulnerability in the self-image is more true about younger adolescents (ages 15 and under) than about older ones (ages 16 and older). Although adolescents' feelings about

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

themselves fluctuate, particularly during the early and middle adolescent years (ages 11 through 15), self-esteem either remains at about the same level or increases gradually over the course of middle and late adolescence and between late adolescence and young adulthood (Block & Robins, 1993; Harter, 1990; Nottelmann, 1987; O'Malley & Bachman, 1983; Rosenberg, 1986; Savin-Williams & Demo, 1984). In addition, self-esteem tends to become increasingly more stable with age, suggesting that adolescents' feelings about themselves gradually consolidate over time and become less likely to fluctuate in response to different experiences (Alasker & Olweus, 1992). In general, the most marked fluctuations in self-esteem and the most heightened feelings of self-consciousness occur during the first half of adolescence, rather than over the course of adolescence itself (Simmons, Rosenberg, & Rosenberg, 1973).

We know of no systematic research examining the direct link between self-esteem and either judgment or decision making. However, to the extent that research on self-esteem indicates that a full consolidation of the self-image does not occur until the last few years of the adolescent decade, we may cautiously conclude that late adolescence may be a time of important gains in maturity of judgment. In some respects, the pattern here is not unlike that observed in the Eriksonian studies of identity development, although the consolidation of self-esteem may occur somewhat earlier and may take place more gradually than the consolidation of identity. By either measure, however, it seems clear that older adolescents (ages 16 through 19) have a more mature sense of self than do younger ones, but it seems clear, as well, that gains in self-esteem and identity consolidation continue during the transition into one's twenties.

Ego Development

A third framework within which responsibility has been studied draws heavily on psychoanalytic theories of ego development. According to these theories (e.g., Blos, 1979; Freud, 1958; Loevinger, 1976), a central developmental task of early adolescence is the establishment of an "individuated" sense of self—a self that is not completely bound up in the child's bond with his or her parents but that has internalized their values and standards nonetheless.

The process of individuation occurs in three distinct phases. During childhood and preadolescence, the sense of self is defined entirely through attachment to parental figures, and decision making is guided primarily by the desire for parental approval. While such decisions might be viewed as competent by parents, they result not from mature judgment, but from compliance with parental wishes. During early adolescence, the individual actively seeks to separate from his or her parents (in some theories, this separation is referred to as "detachment," in others, as individuation). This separation may be manifested as oppositionalism, rebellion, or rejection of parental advice. While adolescents may seem more "independent" than before, their decisions are still determined by parental wishes (albeit oppositionally), and are not a product of reasoned judgment. Not until the adolescent has worked through the individuation process will the young person demonstrate independent

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

judgment that is based neither on echoing nor defying parental sentiment. In theory, once the adolescent has developed a healthy sense of individuation, he or she can act *truly* independently, in the sense that he or she is free to agree or disagree with parental wishes. Decisions might be influenced by parental advice, but they are not be not determined by it (in either a conforming or opposing sense).

Blos's theory of individuation is widely cited, but it has not generated very much empirical research. Most of the evidence relevant to the subject of maturity of judgment comes from clinical anecdote and parental observation, both of which mark early adolescence as a time of exceptionally poor judgment, if not perhaps excessive oppositionalism. Nevertheless, there are no studies that directly investigate the links between individuation and decision making, and no studies that examine the proposition that maturity of judgment does not arrive on the developmental scene until the process of individuation is complete.

Research on age differences in individuation is also sparse. The few studies that have reported age differences suggest that individuals become more individuated with age (e.g., Steinberg & Silverberg, 1986). Interestingly, and in contrast to the view that the main "work" of individuation is over by middle adolescence, these studies show continued increases in emotional autonomy throughout the adolescent years. Unfortunately, in the absence of research on the relation between individuation and judgment, it is not clear how to interpret these age trends. Individuation in early adolescence would be expected to be associated with *immaturity* of judgment, whereas individuation late in adolescence would be expected to be associated with maturity.

A related perspective derives from the work of Loevinger (1976), who has attempted to map out the progression of ego development over the life-span. In Loevinger's model, the development of the ego is reflected in the internalization of the rules of social intercourse, cognitive complexity, and objectivity. In addition, individuals' impulse control becomes guided by personal intentions (rather than regulated by others, such as parents), and individuals develop greater self-awareness and the capacity for more mature, more reciprocal interpersonal relationships. Given these characteristics of ego maturity, it is reasonable to hypothesize that an individual functioning at a higher level of ego development would demonstrate greater maturity of judgment than would one functioning at a lower level. Consistent with this, scores on measures of ego development have been shown to be predictive of reasoning in social and moral situations. In fact, ego development is a better predictor of social reasoning (i.e., reasoning about social situations or interpersonal problems) than are other developmental markers, including chronological age or logical reasoning ability (Blanchard-Fields, 1986). This suggests that an assessment of individuals' ego development may in fact provide insight into decision-making processes above and beyond that gained from the assessment of cognitive skills alone.

Studies of the relation between chronological age and ego development show predictable shifts between early and middle adolescence (i.e., during the period from 12 to 16), but not between late adolescence and young adulthood (i.e., during the period from 17 to 25). Thus, up through middle adolescence, there are predictable patterns of developmental change, with movement to higher levels of ego

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

functioning more or less universal among psychologically healthy individuals. But after middle adolescence, variation in ego development scores appears more useful for understanding individual differences in psychological functioning than for understanding age differences (Foster & Sprinthall, 1992; Noam & Dill, 1991; Noam, 1992). Once they have reached age 17 or so, most adolescents function at the same level as do the majority of adults. This general pattern—clear differences between younger and older adolescents, few differences between older adolescents and young adults—is consistent with what one might predict from Blos' theory of individuation, which suggests as well that the main developmental work in this domain is accomplished during early and middle, rather than late, adolescence. Nevertheless, without research linking individuation to decision making, conclusions regarding maturity of judgment cannot be drawn.

Summary

Research on the development of responsibility in adolescence suggests several provocative and researchable questions about the link between this aspect of adolescents' psychosocial development and their maturity of judgment, but it answers few of them. Although no research has systematically examined the links between various aspects of autonomy, identity, or ego development, on the one hand, and maturity of judgment, on the other, indirect evidence and theories of adolescent development suggest that such studies may be profitable.

There is insufficient research on the developmental course of responsibility in adolescence and young adulthood to draw definitive conclusions about age differences in maturity of judgment that may be related to age differences in responsibility. Although numerous studies have documented development of responsibility during the early and middle adolescent years, few studies have spanned adolescence and young adulthood, leaving open the question of whether gains in responsibility continue beyond high school and, if so, whether there are important transition points that might point to specific chronological ages at which relatively more sizeable shifts in responsibility occur. More research is needed before any practical application of this work can be drawn.

THE DEVELOPMENT OF TEMPERANCE

The relatively high prevalence of willful engagement in dangerous activities during adolescence has suggested to some observers that teenagers may have more difficulty than adults in controlling their impulses. The higher prevalence of willful risk taking in adolescence is not because adolescents do not perceive risks where adults see them. Indeed, there is substantial evidence that adolescents are well aware of the risks they take (Alexander, Kim, Ensminger, Johnson, Smith, & Dolan, 1990).

There is no single explanation for risk-taking that occurs when the individual knows better, especially in what seem to be obviously dangerous situations. Theo-

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

rists working from a purely cognitive framework (e.g., Furby & Beyth-Marom, 1992) have attempted to explain such risky behavior as the outcome of a decision-making process that factors into the equation such variables as the estimated likelihood of risk, the estimated seriousness of the potential risk, and the costs and benefits of alternative behaviors. Research in this tradition suggests that adolescents and adults employ similar decision-making algorithms but reach different decisions because they attach different weights and valences to the variables used in their calculations (for a summary of relevant studies in this area, see Scott et al., 1995).

We believe that the methodology employed in many of these studies of decision making is inherently limited in its ability to unearth differences in adolescent and adult decision making that have *noncognitive* underpinnings. In particular, the assessment of decision making in controlled laboratory situations that ask individuals to respond to hypothetical situations is likely to diminish (if not eliminate entirely) the role of emotion in moderating cognitive processes. One specific aspect of emotional functioning that is a good candidate for further consideration in this light is what we refer to as *temperance*.

The study of temperance in adolescence stems from research on risk-taking behavior and associated phenomena, such as sensation seeking. Within this broader framework, several arguments have been fashioned to explain why adolescents are more likely than adults to take risks. One position is that sensation seeking increases during adolescence, leading to increased risk taking as a means of achieving excitement. Another viewpoint posits that hormonal and physiological changes that accompany puberty result in higher levels of impulsivity and recklessness. Finally, a third perspective emphasizes the influence of emotion and mood on decision making. Because adolescents are thought to be more volatile in their in mood, it has been suggested that their decision-making abilities may be frequently compromised.

Sensation Seeking

Sensation seeking has been defined as a tendency to seek out intense, varied, and novel activities (Zuckerman, 1979). Individuals high in sensation seeking are more oriented toward impulsive, antisocial, and nonconformist behavior (Zuckerman & Link, 1968). Because sensation seeking may be one of the developmental contributors to risk taking, some researchers have predicted that its manifestation should be greatest during adolescence (Arnett, 1992). Accordingly, it is important to understand the influence of sensation seeking on adolescent behavior and to determine whether sensation seeking interferes with individuals' ability to make mature judgments.

Given the widely held stereotype of adolescents as more impulsive than adults, it is ironic that we know much more about the developmental course of impulsivity prior to middle adolescence than we do about its course after this age. Most research indicates no reliable age differences in impulsivity among individuals between the ages of 4 and 16 (Achenbach & Edelbrock, 1981; Susman, Inoff-Germain, Nottelmann, Loriaux, Cutler, & Chrousos, 1987), although impulse control may fluctuate more during early adolescence than before (Abramowitz, Petersen, &

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

Schulenberg, 1984). The few extant comparisons of adults and adolescents suggest that thrill seeking and disinhibition (as assessed via measures of sensation seeking) may be higher during adolescence than adulthood (Giambra, Camp, & Grodsky, 1992; Zuckerman, Eysenck, and Eysenck, 1978). Taken together, these studies suggest that impulsivity may be stable during childhood and middle adolescence (until age 16), increase between middle and late adolescence (until age 19), and then decline over the course of adulthood. In light of the paucity of developmental research beyond age 16, however, this suggestion must be viewed with great caution. Furthermore, these studies do not investigate the relation between sensation seeking and judgmental maturity, so increases in sensation seeking may not necessarily reflect changes in maturity of judgement.

Pubertal Maturation and Judgment

A different angle on the question of adolescent impulsivity comes from studies of puberty and its effects on mood and behavior. Adolescence has long been considered a time of storm and stress, during which adolescents are victims of "raging" hormones that drastically influence their behavior. According to a recent comprehensive review of research on hormones and adolescent mood and behavior, however, the direct connection between hormones and mood in adolescence is not very strong (Buchanan, Eccles, & Becker, 1992). When studies do find a connection between hormonal changes at puberty and adolescent mood or behavior, the effects are strongest early in puberty, when the system is being "turned on," and when hormonal levels are highly variable. One interpretation of this is that it is not so much the absolute increases in these hormones during puberty that may affect adolescents' moods, but their rapid fluctuation early in puberty (Buchanan et al., 1992). Even still, most researchers agree that the impact of hormonal change on mood and behavior in adolescence is greatly moderated by environmental factors (Brooks-Gunn & Reiter, 1990).

Studies of pubertal change and adolescent behavior indicate the need to take into account the timing of maturation, however. In particular, *early* pubertal maturation may have adverse effects on decision making because early maturers may be placed in more challenging decision-making situations at an earlier age than their later-maturing peers. Early pubertal maturation is associated with more problem behavior among both boys and girls (if not necessarily with immaturity of judgment), including truancy, delinquency, school misconduct, cigarette smoking, drug and alcohol use, and early sexual intercourse (e.g., Aro & Taipale, 1987; Magnusson, Stattin, & Allen, 1986). The link between early physical maturation and increased problem behavior is attributable to the more frequent contact of early maturing adolescents with older peers (Magnusson et al., 1986). To the extent that early maturation places individuals in riskier contexts at a younger age than would otherwise be expected, puberty may contribute to poorer judgment among young adolescents who are physically advanced for their age.

Thus, while it is unlikely that hormonal changes at puberty have a direct impact on decision-making skills, there is some evidence that these endocrine changes

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

can affect judgment indirectly, through their effect on adolescents' emotional states, their susceptibility to other stressors, and their social relations (in particular, exposure to older peers). Since maturity of judgment implies the ability to keep emotions from interfering with the decision-making process, it follows that if hormonal fluctuations result in increased emotionality, this may place limits on the level of judgmental maturity attainable by an adolescent whose hormonal levels have yet to reach equilibrium.

Adolescent Moodiness and Judgment

Research on puberty suggests some basis for hypothesizing that adolescent mood states may fluctuate more than those of adults, especially prior to the conclusion of pubertal maturation. Before we discuss how these fluctuations in mood may influence the decision-making processes of adolescents, we first consider how emotions influence decision-making processes more generally.

It is well established that affect plays an important role in cognition. First, being in a good mood has a positive effect on decision-making skills; happy people reach decisions more quickly because they manage information more efficiently (Isen & Means, 1983). Second, positive affect increases risk-taking behavior, but only as long as the risk is relatively low; when the risk is moderate to high, positive affect tends to make people more cautious (Isen & Patrick, 1983; Isen & Geva, 1987). Third, people who are in a good mood are more likely to contemplate the possibility of loss, which contributes to conservative decision making (Isen & Geva, 1987). Thus, although positive affect may make individuals slightly more risk-tolerant, individuals behave cautiously when they perceive risks to be significant enough to destroy their positive mood (Isen & Patrick, 1983; Isen & Geva, 1987; Isen, Nygren, & Ashby, 1988). Less is known about the impact of negative affect on decision making. Some research indicates that negative mood states may make individuals more risk averse (e.g., Deldin & Levin, 1986; Pietromonaco & Rook, 1987), although little is known about the differential effects of different types of negative moods (e.g., anger versus depression). Stress, as well as mood state, has also been shown to influence decision making (see Janis, 1982). Individuals under stress tend to be hypervigilant, which leads to disorganized and faulty decision making.

It is widely believed that, owing both to greater stress and fluctuating hormones, adolescents experience emotional states that are more extreme, more variable, and less predictable than those experienced by children or adults (Larson & Lampman-Petraitis, 1989). Because variations in stress and mood may in fact affect decision making, it is important to ask whether there is any basis in fact for the popular portrait of heightened moodiness in adolescence and, if so, whether there are predictable age changes in moodiness that would inform our discussion of maturity of judgment.

Existing studies suggest that moodiness (more accurately, volatility of mood) may in fact be more characteristic of adolescents than adults. Larson, Csikszentmihalyi, and Graef (1980) obtained direct data on emotional experiences by having

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

adolescents and adults (19–65 years of age) carry electronic pagers to signal subjects to report on their mood and its intensity at various points in the day. Results indicated that adolescents have more rapid and more extreme mood swings (both positive and negative) than adults. In a more recent study, Larson and Lampman-Petraitis (1989) found no age differences in emotional variability among 5th through 9th graders. Taken together, Larson's studies of mood are consistent with findings from studies of impulsivity discussed earlier, namely, that there are no reliable age differences in mood volatility up until age 15 or so, but possible age differences between middle adolescents and adults.

What does this research on adolescent moodiness tell us as far as adolescent judgment is concerned? Because adolescents may report more extremes in both positive and negative affect than adults, the overall effect of variations in mood on age differences in judgment may not be apparent (i.e., any effects of positive mood will be offset by the effects of negative mood). However, given that adolescents' moods are more volatile than adults', one reasonable hypothesis is that adolescents' judgment is less consistent than that of adults. Unfortunately, no studies have been conducted comparing the decision-making abilities of adolescents and adults in similar mood states, nor has any research examined consistency of judgment across decision-making situations as a function of fluctuation in mood or age. Both types of research are needed to determine whether the effects of mood on judgment vary between adolescents and adults.

Summary

Although more research on the development of temperance is needed, preliminary evidence from several rather disparate literatures—on sensation seeking and impulsivity, on moodiness, and on the impact of pubertal hormones on mood and behavior—point in one general direction: Adolescents probably have more difficulty in controlling their impulses than do adults. However, there are too few studies of temperance during late adolescence to draw firm conclusions about the approximate age at which individuals become noticeably less impulsive or less inclined to seek excitement. Studies of pubertal hormones and their impact on adolescents' affective state would seem to suggest that impulsivity should decline when levels of pubertal hormones have stabilized. Further research on impulsivity, sensation-seeking, and mood should chart the development of these traits across a broader range of ages and link these traits specifically to decision-making competence.

THE DEVELOPMENT OF PERSPECTIVE

A third influence on maturity of judgment that potentially may change during adolescence is in the realm of perspective. For purposes of this review, we use the term *perspective* to refer to a set of dispositions that permit the adolescent to frame a decision within a "bigger picture." Perspective, so defined, can take several forms,

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

including the ability to see both short- and long-term consequences (often referred to as "time perspective"), the ability to see how one's actions or decisions affect others (often referred to as "role taking" or "perspective taking"), and the ability to place one decision in the context of others, as when multiple costs and benefits of a single course of action are considered simultaneously—the "cost-benefit calculus" (Scott et al., 1995). Although the growth of perspective is closely related to the development of cognitive abilities, perspective has psychosocial components as well (indeed, in developmental psychology, various components of perspective are studied under the rubric of "social cognition"). In either case, one would expect that an individual might exhibit different levels of perspective in different contexts, and that the development of perspective is strongly influenced by experience as well as maturation.

Decentration

The three aspects of perspective listed above share in common a phenomenon called "decentration," the ability to shift one's focus away from the center of a problem—the center, typically, being oneself (as opposed to others), the immediate situation (as opposed to the future), and the most obvious costs and benefits (as opposed to the less apparent ones). Maturity of judgment, within this framework, implies a greater tendency to decenter in decision-making situations—in other words, to be less egocentric. Research on the development of decentration during adolescence has been heavily influenced by the Piagetian model of adolescent cognitive development.

The Piagetian model of adolescent cognitive development (Inhelder & Piaget, 1958) emphasizes the development of abstract logical reasoning (or, "formal operations," as it is known within Piaget's model) and, more specifically, the transition from concrete to abstract thinking believed to take place during the transition from childhood into adolescence. The development of formal operational thinking enables the adolescent to engage in hypothetical, deductive, and abstract thinking at a level of sophistication not displayed before adolescence. This cognitive ability is, in turn, expected to increase the individual's capacity for decentration (or minimize the individual's tendency toward egocentrism). Abstract thinking appears to develop gradually over the course of adolescence, with performance improving until about age 17 or 18, at which point the performance curve reaches an asymptote—a pattern reminiscent of that found in studies of ego development (Foster & Sprinthall, 1992; Overton, 1994). To the extent that abstract logical reasoning affects decentration, systematic age differences in this disposition should be found up until this age but not thereafter.

Adolescent Egocentrism

Empirical research on adolescent decentration and its converse, egocentrism, has focused, interestingly, on two seemingly contradictory hypotheses: (1) that adolescents' thinking becomes more egocentric, at least in early adolescence (a stance

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

exemplified in studies of such oft-cited phenomena as the "personal fable" and the "imaginary audience"); and (2) that adolescents' perspective taking becomes more decentered, especially in middle and late adolescence (a stance exemplified in research on role taking and moral development).

There is some debate in the literature as to the validity of the first hypothesis. Despite the popular appeal of Elkind's theoretical argument regarding the development of egocentrism (1985), few empirical studies have supported his contention that individuals' tendency toward egocentrism peaks in early adolescence (Gray & Hudson, 1984; Riley, Adams, & Neilsen, 1984). Nor have studies found that adolescents are more egocentric than adults, at least with respect to their vulnerability to the personal fable (Quadrel, Fischoff, & Davis, 1993) or imaginary audience (Goosens, Seiffage-Krenke, & Marcoen, 1992). If anything, individuals become less egocentric between childhood and adolescence, but retain a certain degree of egocentrism throughout adolescence and adulthood.

The focus in research on adolescent decision making on the role of adolescent egocentrism appears somewhat misplaced, since egocentrism is presumed to be a feature of *early* adolescent thought, not adolescent thought in general. Indeed, because egocentrism has been hypothesized to wane after early adolescence, there has been little reason to proceed from the assumption that there are differences in egocentrism between adults and high school aged adolescents. Not surprisingly, then, attempts to link age differences in judgment (beyond middle adolescence) to age differences in egocentrism have not been successful.

Social Perspective Taking and Moral Development

A different avenue of inquiry into the relation between perspective and judgment inheres in studies based on Selman's theory of social perspective taking (Selman, 1980) or Kohlberg's theory of moral development (Kohlberg, 1976). Each of these theories is derived from Piaget's cognitive-developmental model, and each posits a stage-sequential model of social cognitive development from childhood through adulthood. The implicit presumption in each theory is that advances in social cognition enable the individual to act in a more thoughtful, more mature fashion.

In Selman's theory, the development of social perspective taking during adolescence involves the transition into a stage of perspective taking he has labeled "mutual" (which occurs sometime during early or middle adolescence) and the transition into a stage he calls "societal" (which generally takes place sometime during late adolescence, if at all). Mutual perspective taking enables the adolescent to be an objective third party and see how the thoughts or actions of one person can influence those of another. In a decision-making situation, this level of perspective taking would enable the adolescent to understand how a decision might be viewed by another person, even if that view were not the same as his or her own.

The transition into "societal" perspective taking, which occurs at a later point in development, is also relevant to discussions of maturity of judgment. At this level, the individual understands that the perspectives people have on each other

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

are complicated and influenced by larger forces than individuals can control, including social institutions and social roles. Thus, for example, an adolescent girl who disagrees with someone's advice about a given decision she faces (e.g., whether to abort a pregnancy) would, at the societal level of perspective taking, not only understand that each of them (the adolescent and the advice-giver) could have different points of view, but also have some appreciation of the relation between the advice-giver's point of view and the role he or she occupies (e.g., parent, teacher, boyfriend, physician, etc.). This understanding may be an important attainment as far as maturity of judgment is concerned, since it would enable the individual to better see how individuals in different roles might have particular vested interests in specific outcomes.

Although there are age-related changes in the development of mutual perspective taking, it is not clear that such changes characterize the transition into societal perspective taking, nor is it clear that this sort of perspective taking is employed by many adults (much less adolescents). The pattern seen in studies of social perspective taking is similar to that seen in ego development, namely, that one can document gradual, age-related changes in perspective taking until about age 16 or so, but not thereafter. Variations in perspective taking after age 16 are likely due to individual differences (e.g., in intelligence, education, etc.) and not to developmental change.

Virtually the same conclusion emerges from studies of moral development derived from Kohlberg's theory. Kohlberg's theory posits that individuals develop through qualitatively different stages of moral reasoning over the course of childhood and adolescence, with reasoning progressing from "preconventional" thinking (reasoning in which moral problems are understood purely in terms of the immediate consequences of acting one way or another), through "conventional" thinking (reasoning in which moral problems are understood in terms of how various courses of action are viewed by others, especially in relation to social rules and conventions), to "postconventional" thinking (reasoning in which moral problems are viewed in terms of abstract moral principles and matters of personal conscience).

Research on the development of moral reasoning is clearly relevant to the study of maturity of judgment, since one notion implicit in Kohlberg's theory is that higher stages of moral development are in fact more "mature." Individuals who reason at higher levels of moral development are, by definition, better able to place a moral problem within the context of the "bigger picture," whether that picture is one that merely includes other people and their evaluations (as in the conventional stage) or moral principles that operate at the societal level (as in the postconventional stage). There is also some evidence that individuals who reason at higher levels of moral development are in fact less likely to commit antisocial acts, less likely to conform to the pressures of others, and more likely to behave prosocially (Rest, 1983).

Moral development, like the development of logical reasoning, proceeds in a gradual fashion, with developmental differences in moral reasoning more striking in childhood and early adolescence than in late adolescence or young adulthood. During childhood, most individuals are preconventional in their reasoning, but by middle adolescence, most individuals reason at the conventional stage of develop-

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

ment most of the time. Conventional moral reasoning also dominates the thinking of the vast majority of adults, however, suggesting an asymptote in moral reasoning for the majority of the population sometime during the middle high-school years. Postconventional reasoning, if it appears at all, does not appear before age 20, and typically only among the very educated (Colby, Kohlberg, Gibbs, & Lieberman, 1983).

Future Time Perspective

Some research has examined yet another component of perspective potentially relevant to the development of maturity of judgment, namely, future-time perspective. Future-time perspective refers to the ability to project events to more distant points in the future. In theory, individuals who are better able to do this will make judgments that take into account long-term as well as short-term consequences, a component of more mature decision making.

Between childhood and young adulthood, individuals become more future-oriented (Greene, 1986; Nurmi, 1991). Gains take place both between childhood and adolescence (e.g., between the ages of 11 and 18) and between adolescence and young adulthood (e.g., between the ages of 16 and 22), especially with respect to how far into the future individuals are likely to project various events. There is insufficient research to draw conclusions about particular ages at which there are especially significant gains in future time perspective, however. Rather, it seems reasonable to hypothesize simply that individuals' capacity for adopting a future time perspective grows gradually from childhood into young adulthood.

Although it is reasonable to speculate that this change in time perspective has implications for decision making (see Scott et al., 1995), it is not clear how to interpret research on developmental changes in future-time orientation, or how to apply these findings to the study of maturity of judgment. The typical assessment tasks measure competence, rather than actual performance; that is, they provide insight into what individuals of different ages *can* do, not what they *actually* do. It may be the case, for example, that when prompted to do so, young adults are more able than adolescents to project events into the future, but this does not necessarily mean that young adults are more likely to adopt a future-time orientation spontaneously within a given decision-making context. Research is needed that more directly assesses age differences in whether and how individuals use a future-time orientation when making decisions, rather than when they are asked to imagine their future selves.

Summary

There is considerable evidence that individuals become less egocentric in their perspective during adolescence. In contrast to research on the development of responsibility, which has generally stopped short of young adulthood, research on the development of perspective (and on the development of the putative cognitive underpinnings of perspective) has examined a wider age span. Based on studies of

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

formal reasoning, social perspective taking, and moral reasoning, we can conclude that there is predictable, gradual growth in these domains between childhood and midadolescence, but that there are few apparent developmental differences beyond that point. This pattern is comparable to that observed in research on ego development.

Research indicates a somewhat different developmental pattern in the development of future-time orientation. Here, studies suggest that development in this domain continues beyond midadolescence, at least through the last year of college. It is important to note, however, that the way in which future-time perspective is assessed severely limits the conclusions one can draw about its relation to judgment in decision-making situations. Because no research has attempted to link changes in perspective directly to changes in maturity of judgment, it is difficult to draw any conclusions about the role that perspective may play in differentiating between the likely decision-making abilities of adolescents and adults.

CONCLUSIONS AND FUTURE DIRECTIONS

In a 1995 article published in this journal, Scott et al. argued that psycholegal research on adolescents' competence ought to be broadened from the informed consent perspective that has shaped empirical work in the area to date. They suggested that researchers pay more attention to the assessment of judgment, broadly defined, and less to the measurement of the cognitive underpinnings of decision making. In the present article, we have built upon Scott et al.'s foundation and proposed a general framework for the evaluation of psychosocial factors that are likely to affect the development of mature judgment. This framework is organized around three sets of psychosocial traits hypothesized to (1) change over development and (2) affect individuals' judgment and decision making: responsibility, temperance, and perspective.

Is there evidence for the widely held assertion under the law that individuals do in fact become more psychologically mature over the course of adolescence? Specifically, do adolescents and adults (or adolescents of different ages) differ in their disposition toward responsibility? In their disposition toward temperance? In their disposition to place things in perspective?

Our review suggests that, with respect to a number of psychosocial characteristics that are likely to influence maturity of judgment, there are in fact significant changes between early and middle adolescence. It should be noted, however, that in most cases, there is little if any research specifically relating these psychosocial characteristics to maturity of judgment. While several analyses of decision making in specific situations have revealed differences between early and middle adolescents (e.g., Ambuel & Rappaport, 1992), the empirical links between psychosocial development and maturity of judgment remain to be established. Also, because few available studies extend beyond the college years, additional research is needed before we can draw conclusions about developmental differences between late adolescence and adulthood.

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

Are the observed age differences in psychosocial characteristics appreciable and consistent enough to warrant the drawing of legal distinctions between adolescents and adults (or among adolescents of different ages) on the basis of differences in maturity? Our impression is that, should the theoretical links between psychosocial characteristics and maturity of judgment be verified, one could justify a distinction between individuals 16 and younger and those 17 and older. We must emphasize that this conclusion is a highly impressionistic one, for while a reasonable reading of the existing evidence supports drawing this distinction with regard to various aspects of psychosocial maturity, studies that specifically examine developmental differences in *judgment* during this age period are lacking, as is research on the links between judgment and psychosocial development. These are two areas of inquiry that need systematic research attention.

Our tentative conclusion that there are important psychosocial differences between early adolescents and adults—differences that probably have implications for judgment—departs from the view that there are "no differences" between adolescents and adults in their decision making, but is consistent with other arguments that distinctions must be drawn between older and younger adolescents (Ambuel & Rappaport, 1992; Belter & Grisso, 1984; Foster & Sprinthall, 1992; Garrison, 1991; Scherer, 1991). Thus there would appear to be a scientific basis within the psychological literature on adolescent development for distinguishing under the law between individuals who have, versus have not, reached the age of 17, at least in present day America (we do not know if these same conclusions would hold in different social and historical contexts). On the question of whether there also are differences between adults and older adolescents that warrant the maintenance of further age-based legal distinctions among individuals 17 and older, we can only conclude that the necessary psychosocial research has not yet been conducted.

Research establishing the relations between psychosocial characteristics and maturity of judgment is needed, also, to determine the extent to which such relations depend upon the particular context in which a given decision is made. It may be, for example, that adolescents exhibit a great deal of perspective when choosing their courses in school, but not when determining whether to abort a pregnancy or whether to waive their *Miranda* rights. It is thus important to determine the extent to which maturity of judgement varies across different decision-making domains.

Our analysis raises three specific methodological concerns to be considered in future research. First, most extant studies evaluate decision making in laboratory experiments that ask individuals to respond to hypothetical situations (Fischoff, 1992). But one of the obvious limitations of the use of hypothetical dilemmas in the assessment of adolescent decision making is that these laboratory situations minimize the potential effects of psychosocial factors on judgment, especially in the realms of responsibility and temperance. By definition, hypothetical situations do not require an individual to exercise responsibility or self-reliance, because hypothetical situations have no real consequences. By design, hypothetical situations minimize the importance of temperance, because subjects in such experiments are well aware that their decision making is under investigation and are rarely expected to make decisions in the face of pressure of time or the coercion of others. In the real world, adolescents make many decisions that have real and often serious con-

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

sequences, often in the company of others, and typically in contexts that may evoke impulsivity among individuals with little self-control. Controlled laboratory experiments cannot hope to capture the decision-making process that occurs when an adolescent is deciding whether to have intercourse for the first time, whether to abort a pregnancy, or whether to grab a ride home from a party with a friend who has been drinking. Examples of the sort of research needed include work by Ambuel and Rappaport (1992), who studied cognitive competence among teenagers who were visiting a medical clinic for a pregnancy test, and by Lewis (1980), who examined age differences in considerations regarding abortion decisions among subjects awaiting the results of pregnancy tests. Future studies should attempt to examine the ways in which responsibility, temperance, and perspective come into play in these and other real-world settings.

A second methodological implication that follows from our analysis is that comparisons between adults and adolescents should clearly differentiate between early and middle adolescents, on the one hand, and late adolescents, on the other. Numerous studies have purported to show an absence of differences between adolescents and adults in their decision-making behavior. Our review indicates, however, that this conclusion may be valid only when adults are compared to *older* adolescents. Contrasts between adolescents and adults that do not distinguish between older and younger teenagers therefore are likely flawed, and, if possible, data from such studies should be reanalyzed with this distinction in mind (e.g., the appropriate comparison groups might be adults, adolescents 17 and older, and adolescents 16 and younger). Along these lines, we need more systematic research on developmental differences in psychosocial maturity that focus specifically on age differences among 14–21-year-olds. Studies limited to high school students do not follow individuals long enough, and studies of young adults (typically, college undergraduates) do not begin early enough.

Finally, we need more basic research into noncognitive influences on decision making that adopts a developmental perspective. Most of what we know about the impact of noncognitive factors on judgment derives from studies of one age group—college undergraduates. While these studies suggest that variations in emotional states do affect judgment and decision making, they do not tell us whether the links between affect and decision making change with age. It may well be correct that adolescents and adults use similar cognitive processes when making decisions, but it may also be the case that their cognitive processing may be differentially affected by noncognitive factors. Researchers must consider ways of altering current methodologies to better allow for the influence of noncognitive factors and should pursue the development of different approaches to the study of judgment that examine adolescents and young adults in real-life, rather than hypothetical, situations.

ACKNOWLEDGMENTS

Preparation of this article was supported by the MacArthur Foundation Research Network on Mental Health and the Law. We are grateful to John Monahan for his comments on an earlier draft of the paper.

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

REFERENCES

Abramowitz, R., Petersen, A., & Schulenberg, J. (1984). Changes in self-image during early adolescence. In D. Offer, E. Ostrov, & K. Howard (Eds.), *Patterns of adolescent self-image: New directions for mental health services* (No. 22, pp. 19–28). San Francisco: Jossey-Bass.

Achenbach, T., & Edelbrock, C. (1981). Behavioral problems and competencies reported by parents of normal and disturbed children aged four through 16. *Monographs of the Society for Research in Child Development, 46*.

Adams, G., Gullotta, T., & Montemayor, R. (Eds.) (1992). *Adolescent identity formation*. Newbury Park, CA: Sage.

Adams, G., & Jones, R. (1983). Female adolescents' identity development: Age comparisons and perceived child-rearing experience. *Developmental Psychology, 19*, 249–256.

Alasker, F., & Olweus, D. (1992). Stability of global self-evaluations in early adolescence: A cohort longitudinal study. *Journal of Research on Adolescence, 1*, 123–145.

Alexander, C., Kim, Y., Ensminger, M., Johnson, K., Smith, B. J., & Dolan L. (1990). A measure of risk taking for young adolescents: Reliability and validity assessments. *Journal of Youth and Adolescence, 19*, 559–569.

Ambuel, B., & Rappaport, J. (1992). Developmental trends in adolescents' psychological and legal competence to consent to abortion. *Law and Human Behavior, 16*, 129–154.

Archer, S. (1982). The lower age boundaries of identity development. *Child Development, 53*, 1551–1556.

Arnett, J. (1992). Reckless behavior in adolescence: A developmental perspective. *Developmental Review, 12*, 391–409.

Aro, H., & Taipale, V. (1987). The impact of timing on psychosomatic symptoms among fourteen to sixteen-year-old Finnish girls. *Child Development, 58*, 261–268.

Asch, S. (1955). Opinions and social pressure. *Scientific American, 193*, 31–35.

Belter, R., & Grisso, T. (1984). Children's recognition of rights violations in counseling. *Professional Psychology: Research and Practice, 15*, 899–910.

Berndt, T. (1979). Developmental changes in conformity to peers and parents. *Developmental Psychology, 15*, 608–616.

Blanchard-Fields, F. (1986). Reasoning on social dilemmas varying in emotional saliency: An adult developmental perspective. *Psychology and Aging, 1*, 325–333.

Block, J., & Robins, R. (1993). A longitudinal study of consistency and change in self-esteem from early adolescence to early adulthood. *Child Development, 64*, 909–923.

Blos, P. (1979). *The adolescent passage*. New York: International Universities Press.

Brittain, C. (1963). Adolescent choices and parent–peer cross-pressures. *American Sociological Review, 28*, 385–391.

Brooks-Gunn, J., & Reiter, E. (1990). The role of pubertal processes. In S. Feldman & G. Elliott (Eds.), *At the threshold: The developing adolescent* (pp. 16–23). Cambridge: Harvard University Press.

Brown, B. (1990). Peer groups. In S. Feldman and G. Elliott (Eds.), *At the threshold: The developing adolescent* (pp. 171–196). Cambridge: Harvard University Press.

Buchanan, C., Eccles, J., & Becker, J. (1992). Are adolescents victims of raging hormones?: Evidence for activational effects of hormones on moods and behavior at adolescence. *Psychological Bulletin, 111*, 62–107.

Colby, A., Kohlberg, L., Gibbs, J., & Lieberman, M. (1983). A longitudinal study of moral judgment. *Monographs of the Society for Research in Child Development, 48* (Serial No. 200).

Cottle, T. (1977). The time of youth. In A. Wessman and B. Gorman (Eds.), *The personal experience of time*. New York: Plenum.

Culver, C. (1982). *Philosophy in medicine*. New York: Oxford University Press.

Deldin, P., & Levin, I. (1986). The effect of mood induction in a risky decision-making task. *Bulletin of the Psychonomic Society, 24*, 4–6.

Elkind, D. (1985). Egocentrism redux. *Developmental Review, 5*, 218–226.

Erikson, E. (1968). *Identity: Youth and crisis*. New York: Norton.

Fischoff, B. (1992). Risk taking: A developmental perspective. In J. Yates (Ed.), *Risk-taking behavior* (pp. 133–162). New York: Wiley.

Foster, V., & Sprinthall, N. (1992). Developmental profiles of adolescents and young adults choosing abortion: Stage sequence, décalage, and implications for policy. *Adolescence, 27*, 655–673.

Freud, A. (1958). Adolescence. *Psychoanalytic Study of the Child, 13*, 255–278.

Furby, M., & Beyth-Marom, R. (1992). Risk-taking in adolescence: A decision-making perspective. *Developmental Review, 12*, 1–44.

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

Garrison, E. (1991). Children's competence to participate in divorce custody decisions. *Journal of Clinical Child Psychology, 20*, 78–87.

Giambra, L., Camp, C., & Grodsky, A. (1992). Curiosity and stimulation seeking across the adult life span: Cross sectional and 6 to 8 year longitudinal findings. *Psychology and Aging, 7*, 150–157.

Gittler, J., Quigley-Rick, M., & Saks, M. (1990). *Adolescent health care decision making: The law and public policy*. Washington, DC: Carnegie Council on Adolescent Development.

Goossens, L., Seiffge-Krenke, I., & Marcoen, A. (1992, March). *The many faces of adolescent egocentrism: Two European replications*. Paper presented at the biennial meetings of the Society for Research on Adolescence, Washington.

Gray, W., & Hudson, L. (1984). Formal operations and the imaginary audience. *Developmental Psychology, 20*, 619–627.

Greenberger, E. (1982). Education and the acquisition of psychosocial maturity. In D. McClelland (Ed.), *The development of social maturity* (pp. 155–189). New York: Irvington Publishers.

Greenberger, E., & Sorensen, A. (1974). Toward a concept of psychosocial maturity. *Journal of Youth and Adolescence, 3*, 329–358.

Greene, A. (1986). Future-time perspective in adolescence: The present of things future revisited. *Journal of Youth and Adolescence, 15*, 99–113.

Grisso, T., & Vierling, L. (1978). Minors' consent to treatment: A developmental perspective. *Professional Psychology, 9*, 412–427.

Harter, S. (1990). Identity and self development. In S. Feldman and G. Elliott (Eds.), *At the threshold: The developing adolescent* (pp. 352–387). Cambridge: Harvard University Press.

Inhelder, B., & Piaget, J. (1958). *The growth of logical thinking from childhood to adolescence*. New York: Basic Books.

Irwin, C., & Millstein, S. (1992). Risk-taking behaviors and biopsychosocial development during adolescence. In E. Susman, L. Feagans, & W. Ray (Eds.), *Emotion, cognition, and development in children and adolescents* (pp. 75–102). Hillsdale, NJ: Erlbaum.

Isen, A., & Geva, N. (1987). The influence of positive affect on acceptable level of risk: The person with a large canoe has a large worry. *Organizational Behavior and Human Decision Processes, 39*, 145–154.

Isen, A., & Means, B. (1983). The influence of positive affect on decision making strategy. *Social Cognition, 2*, 18–31.

Isen, A., Nygren, T., & Ashby, F. G. (1988). Influence of positive affect on the subjective utility of gains and losses: It is just not worth the risk. *Journal of Personality and Social Psychology, 5*, 710–717.

Isen, A., & Patrick, R. (1983). The effect of positive feelings on risk taking: When the chips are down. *Organizational Behavior and Human Performance, 31*, 194–202.

Janis, I. (1982). Decision making under stress. In L. Goldberger & S. Breznitz (Eds.), *Handbook of stress: Theoretical and clinical aspects* (pp. 69–80). New York: Van Nostrand Reinhold.

Josselson, R. (1980). Ego development in adolescence. In J. Adelson (Ed.), *Handbook of adolescent psychology* (pp. 188–210). New York: Wiley.

Kohlberg, L. (1976). Moral stages and moralization: The cognitive-developmental approach. In T. Lickona (Ed.), *Moral development and behavior*. New York: Holt, Rinehart & Winston.

Larson, R., Csikszentmihalyi, M., & Graef, R. (1980). Mood variability and the psychosocial adjustment of adolescents. *Journal of Youth and Adolescence, 9*, 469–490.

Larson, R., & Lampman-Petraitis, C. (1989). Daily emotional states as reported by children and adolescents. *Child Development, 60*, 1250–1260.

Lewis, C. (1980). A comparison of minors' and adults' pregnancy decisions. *American Journal of Orthopsychiatry, 50*, 446–453.

Lewis, C. (1981). How adolescents approach decisions: Changes over grades seven to twelve and policy implications. *Child Development, 52*, 538–544.

Loevinger, J. (1976). *Ego development*. San Francisco: Jossey-Bass.

Mack, J. (1909). The juvenile court. *Harvard Law Review, 23*, 104–119.

Magnusson, D., Stattin, H., & Allen, V. (1986). Differential maturation among girls and its relation to social adjustment in a longitudinal perspective. In P. Baltes, D. Featherman, & R. Lerner (Eds.), *Life span development and behavior* (Vol. 7, pp. 135–172). Hillsdale, NJ: Erlbaum.

Mann, L. (1992). Stress, affect, and risk taking. In J. Yates (Ed.), *Risk-taking behavior* (pp. 201–230). New York: Wiley.

Marcia, J. (1980). Identity in adolescence. In J. Adelson (Ed.), *Handbook of adolescent psychology*. New York: Wiley.

Marks, F. (1975). Detours on the road to maturity: A view of the legal conception of growing up and letting go. *Law and Contemporary Problems, 39*, 78–92.

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

Meisel, A., Roth, L., & Lidz, C. (1977). Toward a model of the legal doctrine on informed consent. *American Journal of Psychiatry, 134*, 285–289.

Montemayor, R., Brown, B., & Adams, G. (1985). *Changes in identity status and psychological adjustment after leaving home and entering college*. Paper presented at the biennial meetings of the Society for Research in Child Development, Toronto.

Murphy, J. (1979). Therapy and the problem of autonomous consent. *International Journal of Law and Psychiatry, 2*, 415–430.

Noam, G. (1992). Development as the aim of clinical intervention. *Development and Psychopathology, 4*, 679–696.

Noam, G., & Dill, D. (1991). Adult development and symptomatology. *Psychiatry, 54*, 208–217.

Nottelmann, E. (1987). Competence and self-esteem during transition from childhood to adolescence. *Developmental Psychology, 23*, 441–450.

Nurcombe, B., & Partlett, D. (1994). *Child mental health and the law*. New York: Free Press.

Nurmi, J. (1991). How do adolescents see their future? A review of the development of future orientation and planning. *Developmental Review, 11*, 1–59.

O'Malley, P., & Bachman, J. (1983). Self-esteem: Change and stability between ages 13 and 23. *Developmental Psychology, 19*, 257–268.

Overton, W. (1994). Personal communication. Department of Psychology, Temple University, Philadelphia, PA.

Pietromonaco, P., & Rook, K. (1987). Decision style in depression: The contribution of perceived risks versus benefits. *Journal of Personality and Social Psychology, 52*, 399–408.

Quadrel, M., Fischhoff, B., & Davis, W. (1993). Adolescent (in)vulnerability. *American Psychologist, 48*, 102–116.

Rest, J. (1983). Morality. In J. Flavell and E. Markman (Eds.), *Handbook of child psychology*. Vol. III: *Cognitive development*. New York: Wiley.

Riley, T., Adams, G., & Neilsen, E. (1984). Adolescent egocentrism: The association among imaginary audience behavior, cognitive development, and parental support and rejection. *Journal of Youth and Adolescence, 13*, 401–438.

Rosenberg, M. (1986). Self concept from middle childhood through adolescence. In J. Suls & A. Greenwald (Eds.), *Psychological perspectives on the self* (Vol. 3). Hillsdale, NJ: Erlbaum.

Savin-Williams, R., & Demo, D. (1984). Developmental change and stability in adolescent self-concept. *Developmental Psychology, 20*, 1100–1110.

Scherer, D. (1991). The capacities of minors to exercise voluntariness in medical treatment decisions. *Law and Human Behavior, 15*, 431–449.

Scherer, D., & Reppucci, N. (1988). Adolescents' capacities to provide voluntary informed consent: The effects of parental influence and medical dilemmas. *Law and Human Behavior, 12*, 123–141.

Scott, E., Reppucci, N., & Woolard, J. (1995). Evaluating adolescent decision making in legal *contexts. Law and Human Behavior, 19*, 221–244.

Selman, R. (1980). *The growth of interpersonal understanding: Developmental and clinical analyses*. New York: Academic Press.

Simmons, R., Rosenberg, F., & Rosenberg, M. (1973). Disturbance in the self-image at adolescence. *American Sociological Review, 38*, 553–568.

Steinberg, L. (1990). Autonomy, conflict, and harmony in the family relationship. In S. Feldman & G. Elliott (Eds.), *At the threshold: The developing adolescent* (pp. 255–276). Cambridge: Harvard University Press.

Steinberg, L., & Silverberg, S. (1986). The vicissitudes of autonomy in early adolescence. *Child Development, 57*, 841–851.

Susman, E., Inhoff-Germain, G., Nottelmann, E., Loriaux, D., Cutler, G., & Chrousos, G. (1987). Hormones, emotional dispositions, and aggressive attributes in young adolescents. *Child Development, 58*, 1114–1134.

Wadlington, W. (1983). Consent to medical treatment for minors: The legal framework. In G. Melton, G. Koocher, & M. Saks (Eds.), *Children's competence to consent* (pp. 57–74). New York: Plenum Press.

Wallace-Broscious, J., Serafica, F., & Osipow, S. (1994). Adolescent career development: Relationships to self-concept and identity status. *Journal of Research on Adolescence, 4*, 127–149.

Zuckerman, M. (1979). *Sensation seeking: Beyond the optimum level of arousal*. Hillsdale, NJ: Erlbaum.

Zuckerman, M., Eysenck, S., & Eysenck, H. (1978). Sensation seeking in England and America: Cross-cultural, age, and sex comparisons. *Journal of Consulting and Clinical Psychology, 46*, 139–149.

Zuckerman, M., & Link, K. (1968). Construct validity for the Sensation Seeking Scale. *Journal of Consulting and Clinical Psychology, 32*, 420–426.

This content downloaded from 76.77.171.85 on Mon, 27 Mar 2017 16:29:48 UTC
All use subject to http://about.jstor.org/terms

REVIEW ARTICLE

Occupational risks and risk perception among Hispanic adolescents

Marta Young†, D. Gary Rischitelli*

ABSTRACT Although child labor laws are designed to protect youth from serious injury in the workplace, there are a number of other factors that influence the effectiveness of occupational injury prevention including adolescent risk perception, failure to understand worker rights, and lack of experience. The growing adolescent Hispanic population in the U.S. is of particular concern because cultural and economic barriers have the potential to further influence these young workers' safety. A greater emphasis on research among Hispanic adolescents is crucial to minimizing adolescent worker injury. To propose effective age and culturally appropriate intervention programs, it will be necessary to understand the knowledge, attitude and beliefs regarding occupational risks within the working adolescent Hispanic community.

Occupational behavioral risk factor perception of Latino adolescents

According to the United States National Institute for Occupational Safety & Health (NIOSH), there are approximately 5.5 million working children between 12 and 17 in the United States. Although there are child labor laws that are designed to protect children from critical injury in the workplace, there are a number of other factors that influence the effectiveness of occupational injury prevention including adolescent risk perception, failure to understand worker rights, and lack of experience. Since 1999, NIOSH has targeted youth workers as a critical population for investigation within their Fatality Assessment and Control Evaluation (FACE) program. The goal is to identify high-risk occupations and provide intervention that will prevent future occurrences of death or serious injury (11). Although adolescent occupational injury has been a topic of investigation for many years, research often fails to address the risk perceptions of adolescents on the job.

The growing adolescent Hispanic population in the U.S. is of particular concern because cultural and economic barriers have the potential to further influence these young workers' safety (note that the term Hispanic refers to all native Spanish-speakers). Data from the U.S. Census Bureau indicates that over 10% of the U.S. population is foreign born, with 40% entering the country in the last decade (17). The U.S. Census Bureau also estimated that in 2002 there were approximately seven million unauthorized immigrants in the U.S., where many are likely to be of Hispanic background. There is a documented total of 38.8 million of Hispanic origin living in the U.S. of a total population of 288.6 million (U.S. Census Bureau). Additionally, Hispanics are more likely to pursue high-risk jobs because they are among the most educationally and economically disadvantaged of the immigrant populations; inadequate access to health care further intensifies this problem (17). Those of Hispanic background have a much higher drop-out rate than other ethnic groups and only 57% of

*To whom correspondence should be addressed: D. Gary Rischitelli, MD, JD, MPH, Assistant Scientist, Oregon Health & Science University Center for Research on Occupational and Environmental Toxicology, 3181 SW Sam Jackson Park Rd. Mailcode L606 Portland, OR 97201
Tel (503) 494-4398 Fax (503) 494-4278
†Claremont McKenna College, Claremont, CA, Summer Student Research Awardee, The Center for Research on Occupational and Environmental Toxicology, Oregon Health & Science University; Portland, OR

Hispanics (age 25 and over) have completed high school (U.S. Census).

With few studies completed that focus on Hispanic adolescents, it becomes even more important to investigate the knowledge, attitudes and beliefs of occupational risks, as well as preventative techniques within this population.

Adolescent Occupational Injury

Adolescent work is generally at minimum wage jobs, such as restaurant work, grocery stores, farms or factories. Studies of adolescent injury show a great majority in retail trade, particularly in eating and drinking establishments (5,6,9,13). The retail trade sector employs 58% of teens between the ages of 15 and 17 (25). Although injury risks are uncommonly identified with retail work, the retail trade sector accounts for the largest proportion of nonfatal work-related injuries (25). Of all injuries, males are also more likely to be injured than females (13). In a statewide study in North Carolina, over half of the 700 teens sampled were injured at least once while on the job; the most frequent injury was caused by a burn (6). Hazards of those in construction or agriculture were ladders, scaffolding, forklifts, tractors, or riding mowers, as well as working around loud noises (6). An additional investigation of occupational adolescent injuries in Minnesota showed 13% of adolescents reported burn injury, of which 44% suffered permanent scarring (9). Part-time or full-time work at irregular hours also puts young workers at risk of fatigue, increasing their susceptibility to occupational related injury.

These examples provide a brief glimpse of adolescent occupations and the associated risks. However, many states in the U.S. lack a comprehensive surveillance system of adolescent occupational injury (5). To specifically address this critical population, NIOSH began investigating adolescent occupational fatalities. From May 1986 to February 2002, the FACE program investigated 59 adolescent occupational deaths collected in 26 different states. The majority of these fatalities occurred in three industries: agriculture, retail trade, and construction (11). According to FACE investigations, the following were common contributors to worker deaths: failure to recognize hazardous situations, absence of safety programs, employer failure to comply with OSHA (Occupational Health and Safety Adminstration) standards or child labor laws, failure to provide safety equipment, lack of appropriate supervision, and learning unsafe behaviors from coworkers (11). Another documentation from 1980 to 1989 recorded 670 adolescent occupational deaths, mainly involving injuries associated with motor vehicles and electrocution (3). The American Centers for Disease Control (CDC) estimates that about 70 adolescents die each year from occupational injury.

To our knowledge, few studies regarding occupational injuries of adolescents have been specifically focused on the Hispanic population. A study was done in a South Texas middle school and high school that was predominantly low-income Hispanic families (21,22). The middle school students were included because younger adolescents may have a greater risk of injury due to lack of job experience, as well as cognitive, psychosocial, and developmental immaturity. Interviews were conducted with 7,302 sixth-eighth graders in school districts located in small towns and rural areas of South Texan counties. Results of the middle school study showed that 56% reported working eight hours per week, while 25% reported occupational injury (22). From surveys of 3,565 high school students in 23 different schools, one third reported working more than 20 hours per week, with the dominant job being restaurant work (21). Both studies showed a significant correlation between intensity of work, especially during the academic year, and increased worker injury (21,22). Results also confirmed previous studies that males are approximately two times more likely to be injured on the job in comparison to females (21). Although it was hypothesized that Hispanics had a greater likelihood to worker injury, the studies actually documented a slightly greater amount of worker injury among non-Hispanic adolescents (21,22). However, it is important to note that Hispanic youth were more susceptible to injury requiring increased medical attention (21). These results are directly related to the type of work; it was found that Hispanics were twice as likely to work in a restaurant than non-Hispanic adolescents, which is a job involving high risk activities (21). Although this investigation involved a community of predominantly lower socioeconomic Hispanics, the studies do not give comprehensive assessment of a possible differential risk among Hispanic adolescents and other ethnic groups.

A further study, although not specifically focused on Hispanic adolescents, surveyed 516 working Hispanics in a community just south of Washington, DC (17). The surveys indicated that safety training was often not provided, and rarely given in Spanish. Additionally, work time lost per injury was 13.75 days per year, which is significantly higher than the national average of only five days (17). Furthermore, 60% of those with work-related injury cases failed to file a worker's compensation claim, caused by situations such as employer discouragement, failure to provide information, or illegal employment (17). Under another study of Hispanic residential construction workers in North Carolina, the following risk factors were

documented: lack of regular safety training, inadequate communication in Spanish, possible discriminatory treatment by employer, worker's lack of knowledge of U.S. safety standards and laws, and financial needs taking precedence over safety (18). Although these study groups do not represent Hispanic adolescents, many of these same risk factors present in the adult working Hispanic population are probably similar or greater among working adolescents in the community.

In addition to the typical adolescent jobs of retail and restaurant work, unique to the Hispanic population is migrant/seasonal work. It is estimated that 7% of the agricultural workforce is composed of adolescents (14). The agricultural workforce is also estimated to be 30% indigenous, creating an increased language barrier because training cannot be understood in English or Spanish. Adolescents in agriculture are at further risk under child labor provisions as well because agricultural child labor laws differ from nonagricultural laws. Children aged 14 to 15 may perform any nonhazardous farm job outside of school hours, children aged 12 to 13 may be employed on their parents' farm or elsewhere with consent, and even children aged 10-11 may be employed in hand-harvest short season crops (10). Normally, youth are covered under child labor laws until age 18; while in agriculture the age is only 16 (11). Four focus groups with 68 Hispanic migrant workers (age range of 16-62) in South Georgia revealed that living conditions were poor, youth were at increased risk of disease, TB, parasites, and pesticide poisoning, and the workers had little knowledge of medical availability and symptoms of common sicknesses or diseases (16). Although Perilla's focus group study does not give concrete prevalence data of associated risks of migrant farm work, it is a glimpse of migrant camp conditions, to which adolescents are often exposed to while working in agriculture. Furthermore, adolescents working in agriculture generally have an education level of only sixth grade or less; therefore, they are rarely aware of concepts such as disease prevention and health precautions (16).

It is obvious that all Hispanic-working adolescents cannot be grouped into one category, as the working population is highly heterogeneous. Migrant farmworkers and day-laborers may be recent immigrants experiencing cultural adjustment and language barriers. However, there is an ever increasing number of U.S. raised, educated bilingual Hispanic adolescents that may be more culturally adjusted to life in the U.S. This particular group has the potential to be drastically different from recent Hispanic immigrants in job selection, view of occupational risk perceptions, education level, and socioeconomic status. If the U.S Hispanic population continues to divert, differences in the Hispanic work force are likely to become more pronounced in the future, making research important not only along ethnic lines, but also important for minimizing adolescent occupational injury within the Hispanic population.

Adolescent Development

Adolescents are also a particularly vulnerable population because they are in the process of undergoing a period of critical development. During adolescent years the reproductive, respiratory, skeletal, immune, and central nervous system develop (8). The biology of the adolescent's body provides an opportunity for toxicants to cause amplified or lasting damage (8,24). For adolescents working in agriculture, those that are exposed to organophosphate pesticides may be more vulnerable. Chronic effects may include asthma, cancer, or neurobehavioral dysfunction; subtle alterations may become manifested in the future (12).

Environmental and family factors also affect adolescents' developmental stages and have the potential to greatly influence adolescents' behavior and cause future problems (23). Risk factors during developmental stages can result in a series of negative consequences and may result in an overall reduced level of health (23). Some of these risk factors may originate from unstable family environments or adolescent maladjustment, which arise or result from factors such as early family responsibility, lower educational achievement, and taxing work or economic events (23). The totality of these stresses may put adolescents at an increased risk of injury at work and result in lasting physical or mental impairment and disability.

Recent studies have investigated the psychological consequences of adolescent part-time employment, challenging previous views that work experience is the most important factor in the socialization of youth to adulthood (2). In general, all factors related to work intensity tend to be negative. For example, working more than 20 hours per week disengages adolescents from school and further provides an opportunity for delinquency and drug use (19).

Protecting Youth at Work (National Research Council, 1998) summarizes the effects of working extensive hours during the school year: increased alcohol, tobacco and drug use, minor delinquency, lack of adequate sleep and exercise, increased rates of dropping out of high school, and decreased overall educational attainment. It is important to note that reducing work hours or leaving the work force leads to increased school performance, but does not reverse previous negative consequences (19). Therefore, it is important to find a work experience that maximizes the benefits of youth work, yet does not promote further

risk of injury or developmental problems.

Adolescent Injury Predictors and Risk Perceptions

When looking at adolescent injury, there are a number of risk factor predictors. In one study, five general categories for predictions of risk factors were identified: demographics, personality, employment, health, and substance abuse (7). Within these categories the significant predictors of work injuries among adolescents were gender, negative affectivity, job tenure, exposure to physical hazards, excessive workloads, job boredom, poor physical health, and on-the-job substance abuse (7). Frone's study documented the following trends in predictors of adolescent occupational injury. Adolescent male injury was found to be more common than female injury; however, results indicated that males are more likely to report on-the-job injury due to greater exposure of occupational hazards and an increased level of on-the-job substance use. Adolescents of high negative affectivity often selected jobs of greater risk. Environmental conditions with physical hazards, heavy workloads, or boring tasks put adolescents at increased risk for injury. Both poor health and depression were found to be related to occupational injury. Finally, direct measurement of on-the-job substance use greatly increases susceptibility to injury. These predictors of adolescent injury should be a key piece of information when developing age-specific intervention and training programs.

Few previous studies have specifically documented occupational risk perception of adolescents; although one was found to actually focus on the Hispanic population's perceptions, it is specific towards farmworker adolescents; therefore, there is lacking data in other occupations. The farmworker study analyzed the risk perceptions of adolescents in agriculture with regard to pesticide exposure (14). It was found that many of these adolescents did not receive pesticide training, nor did they perceive much danger while working in the fields (14).

Additionally, adolescents have a different mentality than adults, making it key to understanding specific adolescent occupational risk perceptions. Previous studies attributed adolescent risk taking to invulnerability or willingness to take risks (4). However, in a comparative study between adults and adolescents, Cohn et al. (1995) revealed that many adolescents do not perceive their actions as unsafe, but instead minimize the amount of risk associated with periodic activities, such as drug use, intoxication, or reckless driving. In another comparative study of adolescent and adult smokers/nonsmokers, a greater percentage of adolescents perceived their risk of addiction lower than others (1). Adolescents were much more likely to hold an optimistic bias that smoking addiction applies to most people, but not to themselves (1). Occasional risk-taking behavior may not result in injury, but this way of thinking may cause teenagers to misinterpret many types of situations (4). This mode of thinking may be transmitted to the workplace and lead to further injury in adolescents.

Intervention Suggestions

Occupational studies show adolescents are put at risk of injury in the workplace. At the same time, the few available studies focusing on the Hispanic population show the possibility of an additional increased risk on-the-job due to cultural and economic barriers.

Furthermore, the common misperceptions of risk by adolescents in dangerous situations are another factor increasing the probability of occupational injury. From these results, it appears that a greater amount of research among Hispanic adolescents is crucial to minimizing adolescent worker injury, as well as documenting the key differential risks among the heterogeneous group of Hispanic adolescents and other working adolescents. This may include a comparison of worker characteristics, injury rates, risky behavior, and risk perceptions between nonagricultural and agricultural Hispanic workers or among Hispanic adolescents and adolescents of differing ethnic groups. To propose effective age and ethnic-specific intervention programs in the workplace, it is first necessary to analyze and understand the knowledge, attitude and beliefs of occupational risks within varying Hispanic adolescent communities and occupations.

REFERENCES

1. Arnett JJ. 2000. Optimistic bias in adolescent and adult smokers and nonsmokers. Addict Behav 25: 625-632.
2. Bachman JG, Schulenberg L. How part-time work intensity relates to drug use, problem behavior, time use, and satisfaction among high school seniors: are these consequences or merely correlates? Dev Psych 1993; 29:220-235.
3. Castillo DN, Landen DD, Layne LA. Occupational injury deaths of 16- and 17-year-olds in the United States. Am J Public Health 1994; 84: 646-649.
4. Cohn LD, Macfarlane S, Yanez C, Imai WK. Risk-perception: differences between adolescents and adults. Health Psychol 1995; 14: 217-222.
5. Cooper SP, Burau KD, Robison TB, Richardson S, Schnitzer PG, Fraser JJ Jr. 1999. Adolescent occupational injuries: Texas, Am J Ind Med 1990-1996; 35: 43-50.
6. Dunn KA, Runyan CW, Cohen LR, Schulman MD. Teens at work: a statewide study of jobs, hazards, and injuries. J Adolesc Health 1998; 22: 19-25.
7. Frone MR. Predictors of work injuries among employed adolescents. J Appl Psychol 1998; 83: 565-576.
8. Golub MS. Adolescent health and the environment. Environ Health Perspect 2000; 108: 355-362.
9. Heinzman M, Thoreson S, McKenzie L, Cook M, Parker D, Carl W. Occupational burns among restaurant workers - Colorado

and Minnesota. MMWR 1993; 42:713-716.
10. Herman AM. 2000. Report on the Youth Labor Force. U.S. Department of Labor.
11. Higgins DN, Tierney J, Hanrahan L. Preventing young worker fatalities. The Fatality Assessment and Control Evaluation (FACE) Program. AAOHN J 2002; 50: 508-514.
12. Landrigan PJ, Garg A. Chronic effects of toxic environmental exposures on children's health. J Toxicol Clin Toxicol 2002; 40: 449-456.
13. Layne LA, Castillo DN, Stout N, Cutlip P. Adolescent occupational injuries requiring hospital emergency department treatment: a nationally representative sample. Am J Public Health 1994; 84: 657-660.
14. McCauley LA, Sticker D, Bryan C, Lasarev MR, Scherer JA. Pesticide knowledge and risk perception among adolescent Latino farmworkers. J Agric Saf Health 2002; 8: 397-409.
15. National Research Council. 1998. Protecting youth at work: health, safety, and development of working children and adolescents in the United States.
16. Perilla JL, Wilson AH, Wold JL, Spencer L. Listening to migrant voices: focus groups on health issues in south Georgia. J Community Health Nurs 1998; 15: 251-263.
17. Pransky G, Moshenberg D, Benjamin K, Portillo S, Thackrey JL, Hill-Fotouhi C. Occupational risks and injuries in non-agricultural immigrant Latino workers. Am J Ind Med 2002; 42: 117-123.
18. Simoyi P, Frederick L, Niezen C, Hobbs G. Latino immigrant workers in residential construction: a qualitative study of risk factors. National Occupational Injury Research Symposium. Pittsburgh, PA. October 17-19, 2000.
19. Steinberg L, Fegley S, Dornbusch SM. Negative impact of part-time work on adolescent adjustment: evidence from a longitudinal study. Dev Psych 1993; 29:171-180.
20. U.S. Census Bureau. 2003. Statistical Abstract of the United States.
21. Weller NF, Cooper SP, Basen-Engquist K, Kelder SH, Tortolero SR. The prevalence and patterns of occupational injury among south Texas high school students. Tex Med 2003a; 99: 52-57.
22. Weller NF, Cooper SP, Tortolero SR, Kelder SH, Hassan S. Work-related injury among south Texas middle school students: prevalence and patterns. South Med J 2003b; 96: 1213-1220.
23. Wickrama KA, Conger RD, Wallace LE, Elder GH Jr. Linking early social risks to impaired physical health during the transition to adulthood. J Health Soc Behav 2003; 44: 61-74.
24. Woolf AD. Health hazards for children at work. J Toxicol Clin Toxicol 2002; 40: 477-482.
25. Zakocs RC, Runyan CW, Schulman MD, Dunn KA, Evensen CT. Improving safety for teens working in the retail trade sector: opportunities and obstacles. Am J Ind Med 1998; 34: 342-350.

Marta Young is a graduate of Claremont McKenna College with a bachelor's degree in Human Biology. She is currently serving as a Peace Corps Volunteer in Peru's community health program, and plans to pursue her interests in studying medicine and international public health when returning to the U.S. next year.